

Single Technology Appraisal

**Pegcetacoplan for treating complement
3 glomerulopathy or primary immune-
complex membranoproliferative
glomerulonephritis in people 12 years
and over [ID6489]**

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pegcetacoplan for treating complement 3 glomerulopathy or primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Contents:

The following documents are made available to stakeholders:

[Access the **final scope** and **final stakeholder list** on the NICE website.](#)

- 1. Company submission from Swedish Orphan Biovitrum Ltd:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
 - a. B30 additional response
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. Kidney Research UK
 - b. MPGN/DDD Support Group
 - c. British Association for Paediatric Nephrology
 - d. Renal Pharmacy Group
 - e. The UK Kidney Association
 - f. National Renal Complement Therapeutics Centre
 - g. NHS England
- 4. Expert personal perspectives from:**
 - a. Dr Sally Johnson, Consultant Paediatric Nephrologist – clinical expert, nominated by British Association for Paediatric Nephrology
 - b. Dr Edwin Wong, Consultant Nephrologist – Clinical expert, nominated by MPGN/DDD Support Group and The UK Kidney Association
 - c. Alex Gibbs - Patient expert, nominated by MPGN/DDD Support Group
 - d. Lewis Brimble - Patient expert, nominated by MPGN/DDD Support Group
- 5. External Assessment Report prepared by KSR**
- 6. External Assessment Report – factual accuracy check**
- 7. Managed access feasibility assessment**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Company evidence submission

September 2025

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Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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Abbreviations

Acronym	Definition
ACEi	Angiotensin-Converting Enzyme inhibitor
ACIP	Advisory Committee on Immunization Practices
ACR	Albumin-to-Creatinine Ratio
ADA	Anti-Drug Antibody
AE	Adverse Event
AIC	Akaike Information Criterion
ANCOVA	Analysis of Covariance
AP	Alternative Complement Pathway
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BNF	British National Formulary
C3G	C3 Glomerulopathy
C3GN	C3 Glomerulonephritis
CFB	Change From Baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CR	Complete Remission
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
CV	Cardiovascular
DDD	Dense Deposit Disease
DSP	Disease Specific Programme
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMBASE	Excerpta Medica database
EPAR	European Public Assessment Report
ESKD	End Stage Kidney Disease
ESRD	End Stage Renal Disease
EQ-5D-5L	Euro Quality of Life-5 Dimension-5 Levels
EQ-VAS	Euro Quality of Life Visual Analog Scale
EVA	Extravascular Haemolysis
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FIFO	First in First out
FMU	First Morning Urine
FSGS	Focal Segmental Glomerulosclerosis
GFR	Glomerular Filtration Rate
GLOSEN	Spanish Society of Nephrology Working Group on Glomerular Disease

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GP	General Practitioner
HCRU	Healthcare Resource Utilisation
HD	Haemodialysis
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HR	Hazard Ratio
HRD	Healthcare Resource Group
HR-QoL	Health-related Quality of Life
HS	Health State
ICE	Intercurrent Event
ICER	Incremental Cost-Effectiveness Ratio
IC-MPGN	Immune-Complex- Membranoproliferative Glomerulonephritis
IF	Immunofluorescence
Ig	Immunoglobulin
IgAN	IgA Nephropathy
IQR	Inter Quartile Range
IRP	International Recognition Procedure
IS	Immunosuppresant
ITC	Indirect Treatment Comparison
ITT	Intention-To-Treat
IVH	Intravascular Haemolysis
KDQOL	Kidney Disease Quality of Life;
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LS	Least Square
LYG	Life Years Gained
MAC	Membrane Attack Complex
MD	Mean Deviation
MEDLINE	Medical Literature Analysis and Retrieval System Online
MDRD	Modification of Diet in Renal Disease
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
eMIT	electronic Market Information Tool
MeSH	Medical Subject Headings
M/M/c	Markovian arrivals/ Markovian service times/ servers
MPGN	Membranoproliferative Glomerulonephritis
MMF	Mycophenolate Mofetil
MMRM	Mixed-effect model for repeated measures
MYR	Malaysian Ringgit
NCC	National Cost Collection
NeF(s)	Nephritic Factor(s)
NHB	Net Health Benefit
NHS	National Health Service

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NMA	Network Meta Analysis
NR	Not Reported
OLE	Open Label Extension
OLP	Open Label Part
ONS	Office for National Statistics
OOM	Orders of Magnitude
OR	Odds Ratio
PAS	Patient Access Scheme
PEG	Polyethylene Glycol
PD	Peritoneal Dialysis
PICOS	Population, Interventions, Comparisons, Outcomes, and Study design
PP	Per-Protocol Set
PNH	Paroxysmal Nocturnal Haemoglobinuria
PR	Partial Remission
PRISMA	Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RaDaR	Rare Disease Registry
RAS	Renin-Angiotensin System
RCP	Randomised Controlled Part
RD	Risk Difference
RoB	Risk of Bias
RRT	Renal Replacement Therapy
SC	Subcutaneous
SAE	Serious Adverse Event
SE	Standard Error
SGLT-2i	sodium-glucose cotransporter-2 inhibitor
SD	Standard Deviation
SLR	Systematic Literature Review
SoC	Standard of Care
SOC	System Organ Class
T2D	Type-2 Diabetes
TEAEs	Treatment Emergent Adverse Events
THB	Thai Baht
UK	United Kingdom
UKRR	United Kingdom Renal Registry
ULN	Upper Limit of Normal
UPCR	Urinary Protein to Creatinine Ratio
US	United States

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VBA	Visual Basic for Applications

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

1.1 Decision problem

The submission covers the technology's full anticipated marketing authorisation for this indication. Pegcetacoplan (Aspaveli) is expected to be indicated for the treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The decision problem that this submission addresses is outlined in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 years and older with primary C3G or primary IC-MPGN	People aged 12 years and older with primary C3G or primary IC-MPGN	
Intervention	Pegcetacoplan (Aspaveli)	Pegcetacoplan (Aspaveli)	
Comparator(s)	Established clinical management without pegcetacoplan, which may include: • Angiotensin converting enzyme inhibitors • Angiotensin II receptor antagonists • Corticosteroids • Mycophenolate mofetil • Sodium-glucose co-transporter-2 inhibitors (SGLT-2) • Iptacopan (subject to NICE evaluation; in people older than 18 years, for C3G) • Other immunomodulatory treatments In people who have previously had a kidney transplant and who have highly aggressive C3 glomerulopathy recurrence as specified in the NHS England clinical commissioning policy for eculizumab: • Eculizumab	Established clinical management without pegcetacoplan, which may include: • Angiotensin converting enzyme inhibitors • Angiotensin II receptor antagonists • Corticosteroids • Mycophenolate mofetil • Sodium-glucose co-transporter-2 inhibitors (SGLT-2) • Iptacopan (subject to NICE evaluation; in people older than 18 years, for C3G) • Other immunomodulatory treatments In people who have previously had a kidney transplant and who have highly aggressive C3 glomerulopathy recurrence as specified in the NHS England clinical commissioning policy for eculizumab • Eculizumab	Eculizumab is not included in the base case analysis due to the limited evidence regarding its widespread use in clinical practise in the UK and lack of robust data confirming its efficacy in stabilising eGFR and reducing uPCR in patients with C3G.

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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	• Stabilisation of deterioration in eGFR • Reduction in proteinuria • Disease progression (including need for kidney transplant and/or dialysis) • Mortality • Adverse effects of treatment • Health-related quality of life	
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • People who have and have not had a kidney transplant • People with C3G ○ For people with C3G, further subgroups could include C3 glomerulonephritis, dense deposit disease and any specific genetic subtypes of these • People with primary IC-MPGN • Age (12 to 18 years or over 18 years)	• People who have and have not had a kidney transplant • People with C3G • People with primary IC-MPGN • Age (12 to 18 years or over 18 years) • People on concomitant immunosuppression	Clinical data is provided on the subgroups listed in the scope. In addition to the subgroups listed in the final scope, the following subgroup has been included: • People on concomitant immunosuppression All available and relevant information in relation to this subgroup is included in Section .1. The economic model was developed to analyse the subgroups of patients with C3G and primary IC-MPGN, and people on concomitant immunosuppression. However, there is no significant difference in results of the other subgroups, and therefore, the cost-effectiveness would not be expected to be different.
Special considerations including issues related to equity or equality	-	Sobi does not believe there are equality considerations that are likely to impact the recommendations and their appropriateness. However, the committee should consider whether the longer waiting	

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		times faced by Black and Asian people represents a health inequality. A third of people (35 %) waiting for a kidney across the UK are from minority ethnic groups but in 2017/18, of those providing their ethnicity when registering on the NHS Organ Donor Register, only 3.3% were Asian, 1% were black and 2% were mixed race. (1). This may need to be factored in when considering who should be treated and when, to ensure all patients have the best chance.	

1.2 Description of the technology being evaluated

Pegcetacoplan (Aspaveli, APL-2) is a targeted C3 and C3b inhibitor consisting of two 15-amino acid cyclic peptides conjugated to a linear polyethylene glycol molecule to increase its half-life. Pegcetacoplan binds to complement protein C3 and its activation fragment C3b (which are part of the body's defense system called the 'complement system'), thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

Pegcetacoplan acts on multiple key steps of C3 overactivation: it blocks C3 cleavage via alternative, classical or lectin pathways of the complement system; it blocks C3 convertase and the amplification loop of the alternative pathway; and it blocks C3b, preventing glomerular C3 deposition and inhibiting C5 convertase activity and subsequent assembly of C5b-9.

Table 2. Technology being evaluated

UK approved name and brand name	Pegcetacoplan (Aspaveli®)
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
Marketing authorisation/CE mark status	Pegcetacoplan is currently indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. A submission to the EMA was made in February 2025 for the indication being assessed in this appraisal, for the treatment of primary C3G and primary IC-MPGN in people 12 years and over. [REDACTED]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Pegcetacoplan (Aspaveli) is anticipated to be indicated for the treatment of adult and adolescent (aged 12 to 17 years) patients with C3G or IC-MPGN. [REDACTED]

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Method of administration and dosage	Adults of any weight and adolescents weighing ≥ 50 kg receive a subcutaneous infusion of 1080 mg (20 mL) twice weekly. For adolescents weighing 35 to < 50 kg, the first dose is 648 mg (12 mL), the second dose of 810 mg (15 mL), and the maintenance dose is 810 mg (15 mL) twice weekly. For those weighing 30 to < 35 kg, the first and second doses are both 540 mg (10 mL) and the maintenance dose is 648 mg (12 mL) twice weekly.
Additional tests or investigations	A renal biopsy is required for diagnosis of C3G or primary IC-MPGN. No additional tests are required for the administration of pegcetacoplan, although patients are required to be vaccinated against <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , and <i>Haemophilus influenzae</i> before treatment administration
List price and average cost of a course of treatment	List price: £3,100 per 1080mg/20ml vial
Patient access scheme (if applicable)	There is an existing simple patient access scheme (PAS) approved with NHS England. However, the company has applied for a change to this PAS, which is conditional on a positive recommendation for the whole population of this appraisal. This submission is based on the updated PAS price. Net price with updated PAS (): per 1080mg/20ml vial

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

1.3.1 C3G and primary IC-MPGN

C3G and primary (idiopathic) IC-MPGN are rare, chronic kidney diseases that are caused by dysregulation of the complement system at the level of complement 3 (C3). This leads to excessive deposition of C3 activation products (C3 deposits) in the kidney, triggering inflammation and progressive, irreversible damage to the renal parenchyma and impairment of kidney function. (2) This leads to excessive deposition of C3 activation products (C3 deposits) in the kidney, triggering inflammation and progressive, irreversible damage to the renal parenchyma and impairment of kidney function. (2) Unlike other chronic kidney diseases, patients with C3G and primary IC-MPGN are children and young adults, which can place a significant burden on their outlook for the future and their caregivers. (3)

There are currently no approved therapies for adult patients with C3G or any patient with primary IC-MPGN, who must rely on supportive care and treatment with non-specific anti-inflammatory drugs that focus on treating symptoms and have limited efficacy in preventing or delaying disease progression. (4-7) The high risk of progression to kidney failure results in patients eventually requiring life-long dialysis or kidney transplantation. (2, 8, 9) Kidney transplants are not curative as patients frequently recur or have allograft loss. (10)

C3G and primary IC-MPGN are rare diseases, with an estimated incidence of 1-3 cases per million per year. (4, 6). More recent data suggests an estimated annual incidence of 0.3 and 0.9 per million for C3G and primary IC-MPGN, respectively. (11) The estimated prevalence of C3G and primary IC-MPGN is 2.0 per million and 2.2 per million, respectively which equates to approximately 100 C3G and 113 primary IC-MPGN patients in England. Prevalence rates and estimated patients in England were calculated from a longitudinal analysis of UK RaDaR data. (12)

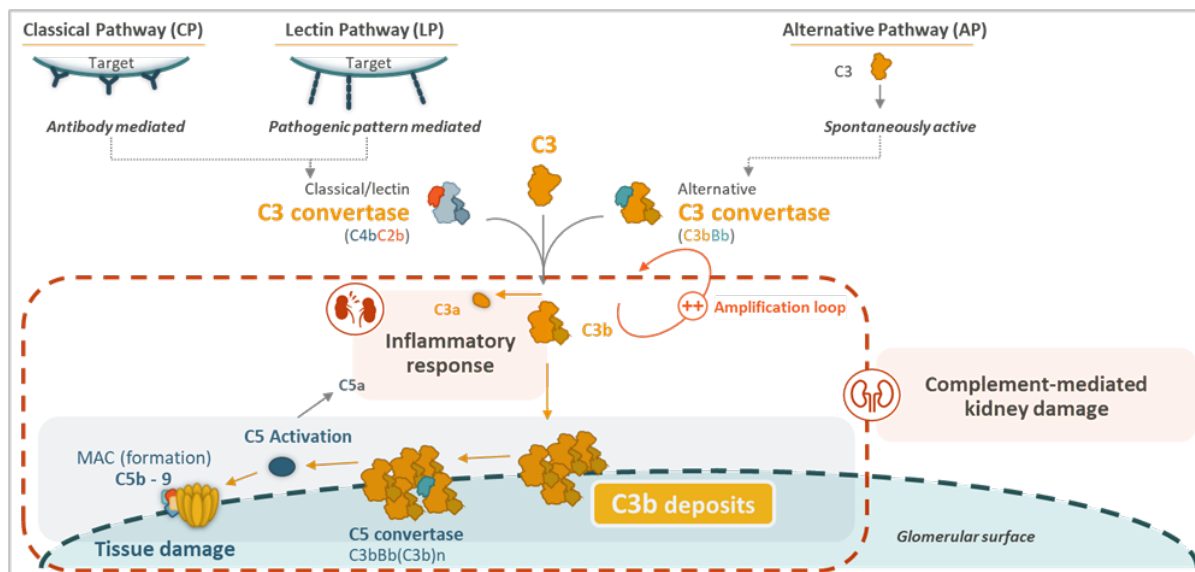
C3G and primary IC-MPGN are distinct but related diseases that can be differentiated through immunofluorescence (IF) staining of renal biopsies, with IC-MPGN demonstrating combined immune complex and C3 deposits, and C3G Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

marked by predominant C3 deposits. (13) C3G has been historically characterised as an alternative pathway disease. Similarly, primary IC-MPGN has been thought to be related to classical complement activation due to the presence of IgG/IgM in the immune complexes found in the glomeruli. However, the true aberrant mechanism that triggers complement dysregulation is not clear for many patients. Regardless of trigger, all C3G and primary IC-MPGN patients have an excessive deposition of C3 activation products (Figure 1). (5, 14)

The accumulation of C3 deposits is associated with the recruitment of inflammatory cells to the glomerular compartments, mesangial expansion due to increased matrix deposition and hypercellularity, capillary wall thickening, and damage to the renal parenchyma leading to disrupted membrane function and causing glomerulonephritis (inflammation of the glomeruli). (15, 16) Glomerulonephritis causes ongoing glomerular injury and rupture of the glomerular basement membrane, detectable by leakage of serum proteins (proteinuria), erythrocytes (haematuria) and leukocytes into the urine. Glomerulonephritis may also present with nephrotic syndrome (massive proteinuria and oedema) if the podocytes are considerably damaged by inflammation. The consequences of persistent glomerulonephritis caused by C3 dysregulation can include scarring, tubular atrophy and glomerulosclerosis, resulting in chronic kidney disease and irreversible kidney failure. (11, 17-19)

Deposition of C3 activation products leads to glomerular inflammation, In addition, serum C3 concentrations are lower than normal in ~50% of patients. (15)

Figure 1. Dysregulation of the complement cascade in C3G and primary IC-MPGN



Abbreviations: MAC= membrane attack complex

C3 dysregulation/overactivation in both disorders can be due to acquired causes, such as auto-antibody that stabilizes the C3 or C5 convertase (C3 or C5 nephritic factors [NeFs]), (13)), genetic and/or environmental factors, but the one consistent factor amongst patients with these conditions is C3 overactivation and deposition in the glomerulus. While the precise cause of complement pathway dysregulation and C3 breakdown product accumulation remains unclear, the disease typically begins with an initial trigger, such as an infection or autoimmune disorder. (18)

1.3.2 Differential classification of C3G and primary IC-MPGN

C3G and primary IC-MPGN are a subgroup of the membranoproliferative glomerulonephritis (MPGN) group of immune-mediated diseases. (20) Both subtypes can be differentiated through immunofluorescence (IF) staining of renal biopsies, with primary IC-MPGN demonstrating combined immune complex and C3 deposits, and C3G marked by predominant C3 deposits. (13)

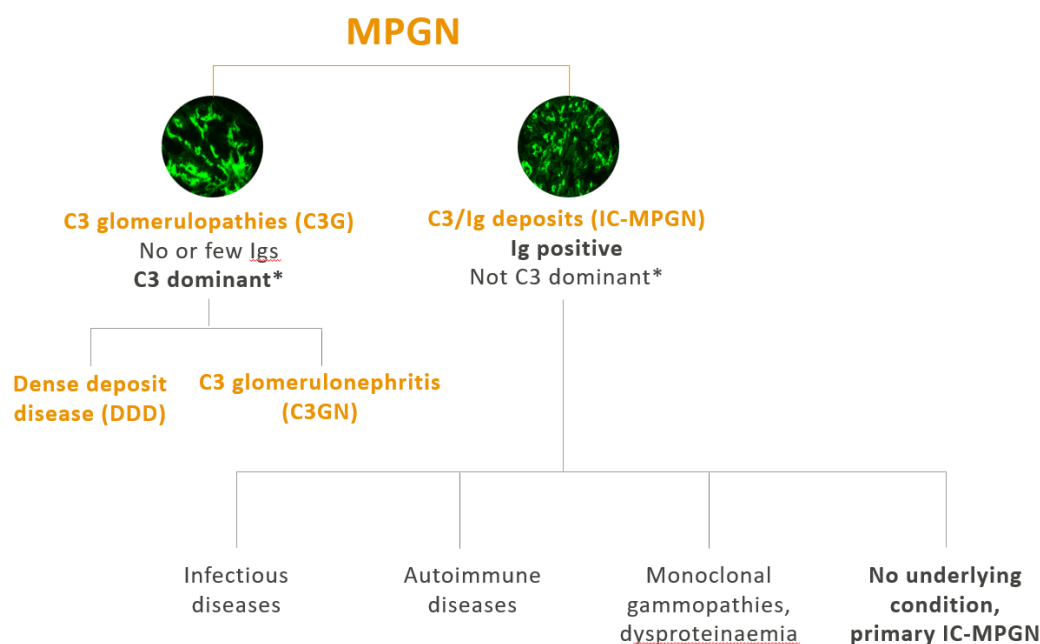
Diagnosing C3G and primary IC-MPGN is challenging because it mimics several other glomerular diseases; therefore, accurate, confirmatory diagnosis requires collaboration with a pathologist, including urinalysis, serology, and biopsy. (2)

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There are 2 subtypes of C3G: dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), which are distinguishable only by renal biopsy. Disease diagnosis is only achieved through biopsy staining for C3c and histopathology analysis through electron microscopy. The clinical presentation, features and disease course are similar between the 2 subtypes, but with some distinctions. DDD tends to present earlier in life than C3GN (median ages of diagnosis for DDD and C3GN are 12 and 26 years old, respectively), and can be more aggressive with faster progression to kidney failure. (21) DDD is also associated with extrarenal manifestations, such as acquired partial lipodystrophy and macular degeneration. The incidence of C3GN is about 3-fold greater than that of DDD. (6, 22, 23)

IC-MPGN can be secondary to autoimmune disease, chronic infections, or a monoclonal gammopathy. If an underlying cause is not identified after the exclusion of all possible secondary conditions, the diagnosis is primary or idiopathic IC-MPGN (24) An overview of MPGN subtypes and their characteristics is shown in Figure 2.

Figure 2. MPGN subtypes and characteristics of C3G and primary IC-MPGN



C3G is triggered by abnormalities in the complement alternative pathway. (2) IC-MPGN is the result of glomerular deposition of immune complexes activated by the complement classical pathway. (24) Primary IC-MPGN is diagnosed after exclusion of secondary conditions. (24) *C3 dominant: C3 is ≥ 2 orders of magnitude stronger than for any other common immune reactant.

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Abbreviations: C3G, complement 3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis.

Primary IC-MPGN has a similar clinical course to that of C3G and other glomerulonephritis. (25, 26) with studies indicating minimal differences in the clinical course or overall survival. (27)

Renal and extrarenal manifestations of disease are like those of other glomerulopathies. Renal disease manifestations include micro- or macroscopic haematuria, light/heavy proteinuria, hypoalbuminemia, reduced eGFR, and foamy urine. (2, 4, 17, 23)

Several extra-renal manifestations include acquired oedema, hypertension, and less commonly partial lipodystrophy, and drusen-like deposits (similar to those seen in age-related macular degeneration but at an earlier age). In addition, psychological symptoms of anxiety, depression, and fatigue are also common. (2, 28)

The disease course is highly variable. Patients can experience acute, episodic disease 'flares' with symptom exacerbation, while others present with a more 'smouldering' disease course, characterised by chronic progression to kidney failure over time. (2, 17) Adult-onset and paediatric-onset patients differ clinically, with children typically experience more disease flares and infectious episodes [109]. However, there are minimal differences in clinical course between C3G and primary IC-MPGN. (27)

C3G and primary IC-MPGN are classified as distinct disease entities. However, for non-specialists, establishing a definitive diagnosis can be challenging due to overlapping clinical and histopathological features. This underscores the critical importance of specialist involvement and oversight in the management of glomerulonephritis to ensure accurate diagnosis.

1.3.3 Renal function and disease progression

1.3.3.1 Proteinuria and risk of disease progression

The severity of proteinuria is a well-established risk factor for progression to kidney failure in many glomerular diseases, including C3G and primary IC-MPGN. (29-35), (36) I

In a recent cohort study of 115 patients with C3G, conducted by the Spanish Society of Nephrology Working Group on Glomerular Disease (GLOSEN), kidney survival was significantly higher in patients with proteinuria <3.5 g/day at diagnosis, regardless of baseline estimated eGFR. (31) The same group used baseline C3G patient features to build a nomogram for predicting the risk of kidney failure at 1, 2, 5, and 10 years. (37) The analysis found that eGFR, baseline proteinuria, and certain histologic features on kidney biopsy (i.e., total chronicity score) were the best objective predictors of kidney survival. The latest analysis of the GLOSEN cohort, which also included patients with primary IC-MPGN (n=51), who were followed up for a median time of 65 months, demonstrated that a ≥50% reduction in proteinuria was associated with a significantly lower risk of kidney failure (HR: 0.61; 95% CI 0.46–0.75, $P < 0.001$). (38)

Furthermore, a recent analysis of longitudinal data from the UK National Registry of Rare Kidney Diseases (RaDaR) registry, which included 287 patients with C3G and primary IC-MPGN found that a 50% reduction in urine protein to creatinine ratio (UPCR) at 12 months, following diagnosis, was strongly associated with a lower long-term risk of kidney failure (adjusted HR 0.33 [95% CI 0.17 - 0.63], $P < 0.001$). (12) In contrast, increases of 20-50% in UPCR at 12 months and declines of 15-20% in eGFR, at 2 years, were strongly associated with eventual kidney failure and progression to kidney failure (HR 0.13 [95%CI 0.03-0.56], $P = 0.007$). Achieving a threshold UPCR of <0.88g/g (<100mg/mmol) by 12 months was particularly strongly associated with lower rate of kidney failure events (HR 0.13 (95% CI 0.03-0.56); $p=0.007$) suggesting that, if proteinuria is shown in clinical trials to be reduced to similarly low levels by therapies that act by reducing disease activity, it is logical to infer that long-term kidney failure hazard will be similarly reduced, supporting the use

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of this accessible end-point in future trials as a surrogate for kidney failure. (12) In support of this, in the VALIANT phase 3 trial, >50% of patients treated with pegcetacoplan for 6 months achieved a UPCR of <1g/g. (39) (manuscript accepted for publication in NEJM) The VALIANT trial is one of the included trials in section 2 of this dossier, and is further summarised in these sections.

Current KDIGO guidelines for C3G and primary IC-MPGN (9) additionally identify 1 g/day of proteinuria (and 0.5g/day for paediatric patients) as an important threshold for stratifying patients and resultant treatment decisions. In support of this, a recent advisory board of clinical experts, sponsored by Sobi, supported >1g/g as a clinically meaningful threshold (Sobi, data on file) (40), which correlated with the pivotal VALIANT trial.

1.3.3.2 eGFR and risk of disease progression

Clinically significant treatment effects on kidney function, measured by eGFR, are similarly expected to predict outcomes in preventing progression to kidney failure among patients with chronic kidney disease (CKD) at high risk of disease progression, including C3G and primary IC-MPGN. (30, 31, 33, 41) In the recent UK RaDaR study, survival was more strongly associated with higher baseline eGFR (≥ 70 mL/min/1.73m²) in comparison to patients with eGFR baselines of 30 – 60 mL/min/1.73m² (HR:0.39; 95% CI 0.19-0.80; P=0.01).(12). Moreover, analysis of outcomes in C3G and primary IC-MPGN demonstrated an association between 24-month eGFR slope and risk of kidney failure. (41) Similarly, in the GLOSEN study of 115 C3G patients, a slower rate of eGFR decline correlated with higher rates of kidney survival. (31)

A pooled analysis of the GLOSEN (n = 117), RaDaR (n =72) and Italian (Mario Negri registry; (42) (n= 50) registries of patients with C3G and primary IC-MPGN investigated clinical and histologic predictors of kidney outcomes in C3G and primary IC-MPGN. (36). The primary outcome was defined as eGFR decline by 30% or progression to ESKD. Over a median follow-up of 3.7 years (interquartile range, IQR [1.2, 6.5]), 89 patients (40%) experienced the primary outcome, with a five-year risk of 35.8 % (95% confidence interval (CI) 29.0%, 43.6%) and no difference in risk

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between those with C3GN, DDD or IC-MPGN. In this multivariable model, lower eGFR, paraprotein presence, and interstitial fibrosis were associated with a higher outcome risk, while native disease (versus recurrence post-transplantation), White ethnicity and lower C4 levels were associated with lower risk. This study also confirms that proteinuria over time is a significant progression predictor: A 50% reduction in proteinuria from baseline to a value less than 1 gram/day (corresponding to UPCR in FMV (0.88 g/g)) was associated with a lower risk of the primary outcome independent of other risk factors (HR 0.35, 95% CI 0.12-0.97).

1.3.4 Treatment goals

Treatment goals should seek to rapidly control proteinuria, while stabilizing eGFR to reduce the risk of disease progression.

The lowering of proteinuria and the maintenance of a stable eGFR have been associated with lower risk of progression to kidney failure and better outcomes in C3G and primary IC-MPGN. As such, the importance of treatments that achieve these outcomes is paramount to the control of these diseases. Given the chronic and irreversible nature of kidney damage in C3G and primary IC-MPGN, control of the disease early in the disease course is optimal. (43)

For proteinuria, achieving below 1 g/d is a robust target to significantly improve kidney outcomes in C3G and primary IC-MPGN. Current KDIGO guidelines for C3G and primary IC-MPGN additionally identify 1 g/d of proteinuria as an important threshold for stratifying patients and resultant treatment decisions. (9) This general target proteinuria range has also been supported by cohort studies such as UK RaDaR which identified significant improvement in outcomes for patients able to reach <0.88 g/d proteinuria. (12) The benefits of lowering proteinuria to below this 1 g/d threshold are likely to be impactful even when demonstrated over periods of time as short as 6-to-12 months, as noted in RaDaR and GLOSEN studies. (12, 38)

This is further supported by a European Delphi expert panel that reached a consensus around using proteinuria as a surrogate marker in C3G and primary IC-MPGN. (Caravaca-Fontán et al., 2025, manuscript submitted for publication) (Sobi, data on file)

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- A threshold of $\geq 50\%$ reduction in proteinuria over 6 months would be considered a clinically meaningful effect of treatment: 94% agreement (30% only 72% agreement)
- A reduction in proteinuria helps to preserve long-term kidney function and as a result is a goal of treatment: 96% agreement
- Longitudinal measures of proteinuria, along with other relevant endpoints (e.g. eGFR) can be used to guide treatment decisions: 100% agreement
- A reduction in proteinuria to < 1 g /day helps to preserve long term kidney function, which is the long-term goal of treatment: 82% agreement

For eGFR, the treatment target of achieving a stable eGFR would be clinically significant as it suggests a treatment is slowing or halting of progressive loss of kidney function. This would expect to predict treatment effects on progression to kidney failure in patients with C3G who are at high risk of disease progression [50]. Studies, such as RaDaR, have strongly suggested the utility of stabilizing eGFR within 2-years. Slowing of eGFR decline in follow up periods of time as short as 6-months has also been shown in select studies to be associated with lower risk of progression; however, there is debate as to whether 6-months is a sufficient duration for eGFR to predict outcomes. (12, 33, 44)

The Kidney Health Initiative (34) convened a panel of experts to reach a consensus on suitable clinical endpoints in C3G. They assessed the data supporting the use of three prespecified trial end points: proteinuria reduction, eGFR stabilisation/improvement and reduction in C3 staining as indicators of treatment response. The C3c deposition immunohistopathology end point was incorporated into the trials because C3 deposits are directly linked to disease pathophysiology and considered causal to kidney impairment. (45) Thus, a reduction in the C3G activity histopathology score was anticipated to be associated with a reduced likelihood of progression of kidney disease.

The panel agreed that a favourable treatment effect on all three endpoints (proteinuria reduction, eGFR stabilisation and histopathological improvement) would Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

provide convincing evidence of efficacy, although complete coherence may not be essential, if there was meaningful lowering of proteinuria and stabilisation or improvement in eGFR. (34)

1.3.5 Clinical outcomes

The clinical burden of C3G and primary IC-MPGN is characterized by progressive, irreversible kidney damage. Patients develop chronic kidney disease (CKD) that may eventually result in kidney failure and ultimately require dialysis and / or repeated kidney transplants. As a result of these clinical burdens, mortality risk in C3G and primary IC-MPGN patient is ~21% higher than the general population. (46-49)

1.3.5.1 Chronic kidney disease

The presence of CKD is common for C3G and primary IC-MPGN patients. From a 2024 ERKReg analysis, among incident patients, 71.7% presented in CKD stage 1 and 6.5% in CKD stage 4/5 for C3G. Incidence of more advanced CKD (Stage 4 or 5) has been shown to be more common in IC-MPGN patients with 27.7% of patients presenting with CKD stage 4/5 and 27.8% with CKD stage 1.(3) CKD is strongly associated with adverse cardiovascular events, with approximately 50% of all patients with CKD stages 4 and 5 having cardiovascular disease. CKD patients have significantly greater risk of fatal atherosclerosis-associated complications including stroke, myocardial infarction, and heart failure. While CKD patients will often have comorbid cardiovascular risk factors such as hypertension, diabetes, and dyslipidaemia the correction of these factors does not neutralize the impact of CKD on cardiovascular risk. (50)

In patients with CKD, comorbid conditions, complications, and major health events all contribute to a lower health-related quality of life and a higher risk of premature death. (44) A collaborative meta-analysis including data from more than 100,000 participants from 21 cohorts (Chronic Kidney Disease Prognosis Consortium 2010), showed increasing risk for all-cause mortality in patients with low eGFR starting from a value of 60 mL/min/1.73 m² compared to those with eGFR values of 75 – 105 mL/min/1.73 m² (HR: 1.18; 95% CI 1.05–1.32), with the risk increasing as eGFR decreased. (51)

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1.3.5.2 Kidney failure

While the rate of progression varies widely across patients, ultimately the progressive loss of kidney function is likely to result in kidney failure. The likelihood of reaching kidney failure in C3G or primary IC-MPGN is similar. It is estimated that approximately 20% of children and 50% of adults with C3G and primary IC-MPGN progress to kidney failure within 10 years after diagnosis. (12, 52, 53)

Kidney failure is associated with significant cardiovascular mortality. Patients with kidney failure have a 10 – 30-fold higher cardiovascular mortality risk and 5 – 10-fold higher stroke risk. In a 2019 study, cardiovascular mortality among young adults aged 22–29 years with incident kidney failure was 143–500 -fold higher than that of otherwise comparable individuals without kidney failure, owing to a very high burden of cardiovascular risk factors. (43, 54) Patients who are in kidney failure will ultimately require dialysis and / or kidney transplantation. It should also be recognised that many patients with C3G and primary IC-MPGN may experience the burdens of kidney failure multiple times as a result of kidney transplantation failure, magnifying the challenges to their QoL as they re-experience the disease course.

1.3.5.3 Dialysis

Most patients who progress to kidney failure will require long term dialysis, which diminishes quality of life and is associated with a higher risk of mortality associated from cardiovascular events and infections. (43) 5-year survival rate of patients on long-term dialysis is 59%. (55)

Mortality is very high among patients on dialysis, especially in the first 3 months following initiation of haemodialysis treatment. Approximately one-quarter of patients on haemodialysis die within a year of initiating therapy in high-income countries, and this proportion is even higher in lower or middle-income countries. (56)

Cardiovascular disease (CVD) is present in >50% of patients undergoing dialysis and the relative risk of death due to CVD events in haemodialysis patients is reported to be 20 times higher than in the general population. In fact, in patients on renal replacement therapy (RRT) the prevalence of coronary heart disease and ventricular hypertrophy has been described to be 40% and 70%, respectively. (57)

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The risk of infection is also markedly greater among patients on dialysis than in the general population, in part driven by access-related infections in patients on haemodialysis with central venous catheters and peritonitis-related infections in patients on peritoneal dialysis.(43, 54)

1.3.5.4 Kidney transplantation

Patients with C3G and primary IC-MPGN will also seek out kidney transplantation as an option for their kidney failure. The prevalence of kidney transplantation is similar between C3G (8 – 32%) and primary IC-MPGN (24%). (12, 49, 58-60). However, kidney transplantation is not a curative treatment approach for these patients. (61)

Kidney transplant in patients with C3G or primary IC-MPGN is associated with a 76% greater risk of mortality vs other nephropathies. (62) Compared with other forms of glomerulonephropathy, patients with C3G or primary IC-MPGN experience significantly higher rates of allograft loss due to disease recurrence, (61), which has been reported in up to ~89% of patients with C3G or primary IC-MPGN; within 37 months. Disease recurrence can occur almost immediately after transplantation in some cases and despite immunosuppressive therapy such as tacrolimus, MMF, and CNIs. (2, 63)

1.3.6 Clinical pathway and current treatment options

There are well-defined clinical guidelines provided by KDIGO for the treatment and management of glomerular disease, including treatment of C3G and primary IC-MPGN. (9) The UK Kidney Association published a commentary on these guidelines in 2023 for managing and treating C3G and primary IC-MPGN. (64) NICE have not produced specific guidelines for these conditions, although guidelines have been published for the management of CKD (65), as well as two evidence summaries, ESUOM49 (66) and ESUOM44 (67), for the use of eculizumab in C3G, in the native kidney and post- transplant, respectively.

An optimal treatment strategy for C3G and primary IC-MPGN using currently available therapeutics has not been established. Similar to disease management for other glomerular diseases, current management for C3G and primary IC-MPGN includes nonspecific measures to manage proteinuria and provide symptom relief. Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

This includes the use of angiotensin inhibition, management of hypertension, hyperlipidaemia, oedema, and other aspects of glomerular disease and CKD. (9, 10) Immunosuppressive therapy is often prescribed, although the choice of drugs and duration of treatment are based on retrospective analyses, limited case series, and observational studies, rather than randomised controlled interventional trials. (10, 66, 67) Treatment escalation involves off-label use of calcineurin inhibitors, mycophenolate mofetil (MMF), anti-CD20 (rituximab) or anti-C5 (e.g., eculizumab) monoclonal antibodies.

To understand the UK C3G/IC-MPGN treatment landscape and patient journey, a recent advisory board of clinical experts (Sobi, dof) (40) stated that in the UK most patients with moderate (1-3 g/d UPCR) or severe (> 3g/d UPCR) C3G or primary IC-MPGN receive systemic treatment for immunosuppression, but would stop treatment if it were ineffective, which is often the case.

Patients with C3G and primary IC-MPGN often continue to experience worsening kidney function or irreversible damage, resulting in a steady progression to end stage kidney disease (ESKD). (2, 53) In adults ~ 50% of patients do not respond to systemic therapy and eventually need dialysis, which is associated with poor outcomes, as outlined in section 1.3.5.3. As well as dialysis, renal transplantation is also an option for patients who reach ESKD (65), although post-transplant disease recurrence is an issue for patients with C3G and primary IC-MPGN. (2, 63) (see section 1.3.5.4).

It is important to recognize that for C3G and primary IC-MPGN, transplantation is significantly less effective as an option to manage disease in comparison to other kidney diseases. C3G and primary IC-MPGN patients may need multiple kidney transplants. In a study of 20 children with C3G and IC-MPGN who had received a kidney transplant, it was the 2nd transplant for 2 patients, and the 3rd transplant for one patient. (68)

In a physician survey as part of the Adelphi Disease Specific Program, 50% of adolescents and 30% of adults with C3G were on a waiting list for kidney transplant

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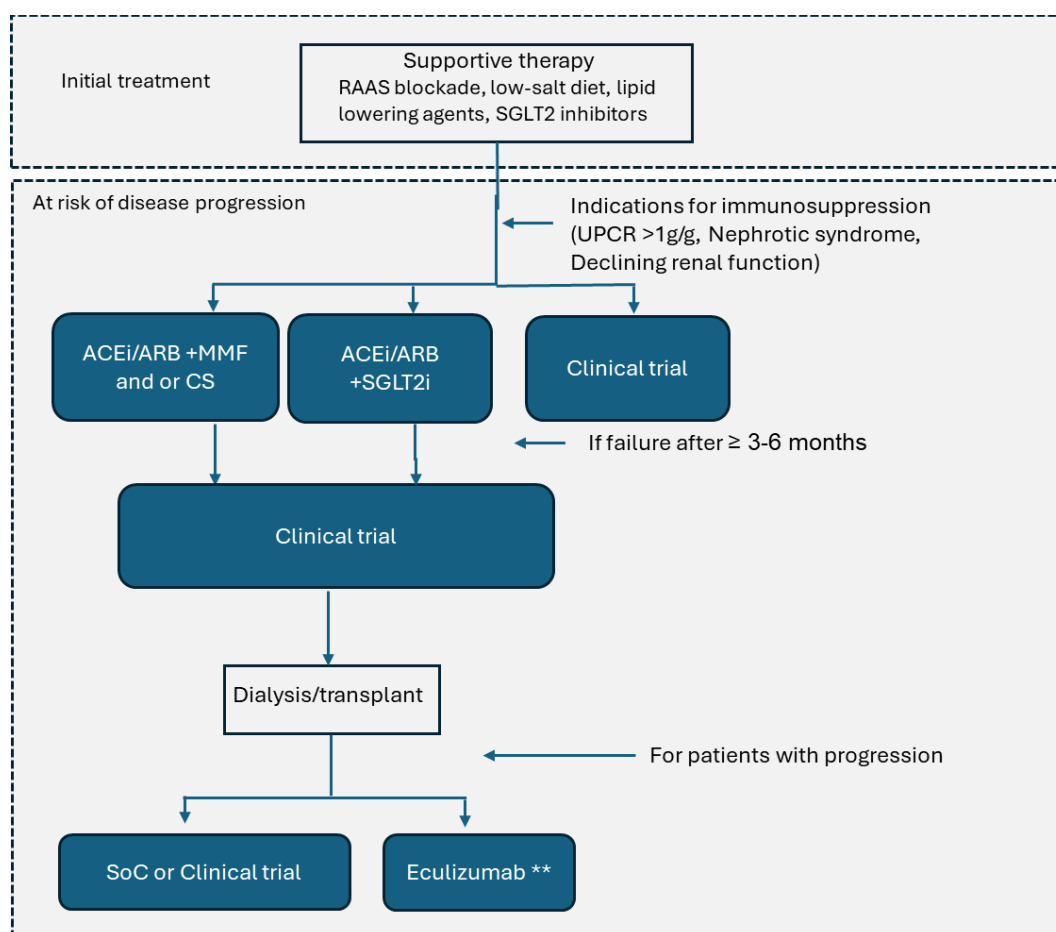
at time of data collection. Similarly, among patients with primary IC-MPGN, 50% of adolescents and 18% of adults were on the waiting list. (69)

In patients with C3G, NICE has produced evidence summaries for the off-label use of eculizumab, both in the native kidney (NICE ESUOM49) (66), and following transplant (NICE ESUOM44). (67) The NICE guidelines acknowledge that patients may not universally respond to eculizumab therapy, as the degree of C5 convertase dysregulation varies between individuals. It should also be noted that NHS England only commissions eculizumab for the recurrence of C3G post-kidney transplant in order to prevent the rapid loss of a transplanted kidney to highly aggressive concurrent disease. (70).

Outside of these treatment options, the KDIGO guidelines indicate that clinicians should consider enrolment in clinical trials for the management of C3G and primary IC-MPGN. (9) Pegcetacoplan has previously been one such option, alongside iptacopan, which is currently undergoing a NICE single technology appraisal for the treatment of adult C3G only. (71)

An overview of the current clinical pathway is shown in Figure 3.

Figure 3. Current treatment pathway for patients with C3G & primary IC-MPGN



Adapted from KDIGO guidelines (9) and NICE evidence summaries [ESUOM49]:C3 glomerulopathy in the native kidney: eculizumab. (66) [ESUOM44]: Prevention of recurrence of C3 glomerulopathy post-transplant: eculizumab. (67)

1.3.7 Unmet medical need

Current best supportive care does not prevent worsening kidney function or irreversible kidney damage, with C3G and primary IC-MPGN patients steadily progressing to ESKD; approximately 50% of patients progress to ESKD within 10 years of diagnosis despite treatment requiring dialysis or transplants (2, 6, 22, 72-76)

Dialysis and kidney transplants are the only options for patients who reach ESKD, but are associated with significant mortality. Kidney transplants are not curative due to high rates of recurrence and subsequent allograft loss (77), (6, 22, 74, 76) Dialysis outcomes are generally poor with ~25% of patients dying within a year and a 5-year survival rate of 59%. (43, 56) Available kidneys for transplants are generally scarce Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

with long waiting lists, (78) thus having a treatment that would delay or avoid the need for kidney transplant would benefit the health care system.

Eculizumab is used off-label for patients with post-transplant recurrent C3G who meet specific criteria, but there is no evidence that it prevents recurrence of C3G. (67) In addition, NHS England only covers the routine commissioning of eculizumab for patients with C3G post-kidney transplant. (70)

It is important to note that there are even fewer treatment options for patients with primary IC-MPGN, as the evidence summaries for eculizumab only cover patients with C3G, and iptacopan is undergoing a single technology appraisal, solely for the treatment of adult C3G patients. (71)

There is a high unmet need in patients with C3G and primary IC-MPGN, and a disease-modifying therapy that can protect the kidneys, native or transplanted, from ongoing damage due to complement hyperactivity by reducing proteinuria and stabilizing eGFR would be a valuable addition to the treatment arsenal.

Given the license for iptacopan covers adult C3G patients only, even the potential addition of this treatment to UK clinical practice would leave an unmet need for adolescent patients with C3G, as well as all those patients with primary IC-MPGN, all of whom would continue to benefit from an additional treatment option.

1.3.8 Pegcetacoplan

Pegcetacoplan is a targeted C3 and C3b inhibitor designed to control C3 overactivation. It provides holistic control of C3 deposits in C3G and primary IC-MPGN by targeting the substrate, the enzyme and the product of C3 dysregulation and inhibiting C3 activation by all complement pathways (alternative, classical and lectin). (79-81)

Pegcetacoplan selectively binds to C3, blocking C3 activation by both C3 convertases of the classical/lectin and alternative pathways, preventing the generation of C3b molecules and the formation of anaphylatoxin C3a. It also inhibits

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the C3 amplification loop by directly blocking the activity and formation of alternative C3 convertase. By binding to C3b, it prevents C3b deposition and induces a decreased density of solid-phase C3b, ceasing the generation of downstream effectors of complement activation on the kidney surface, which lead to inflammation and renal injury (e.g. surface C3 convertases (C3bBb) and C5 convertases). C5 convertase inhibition blocks cleavage of C5, preventing formation of the anaphylatoxin C5a and the membrane attack complex (MAC) (C5b-9). (82)

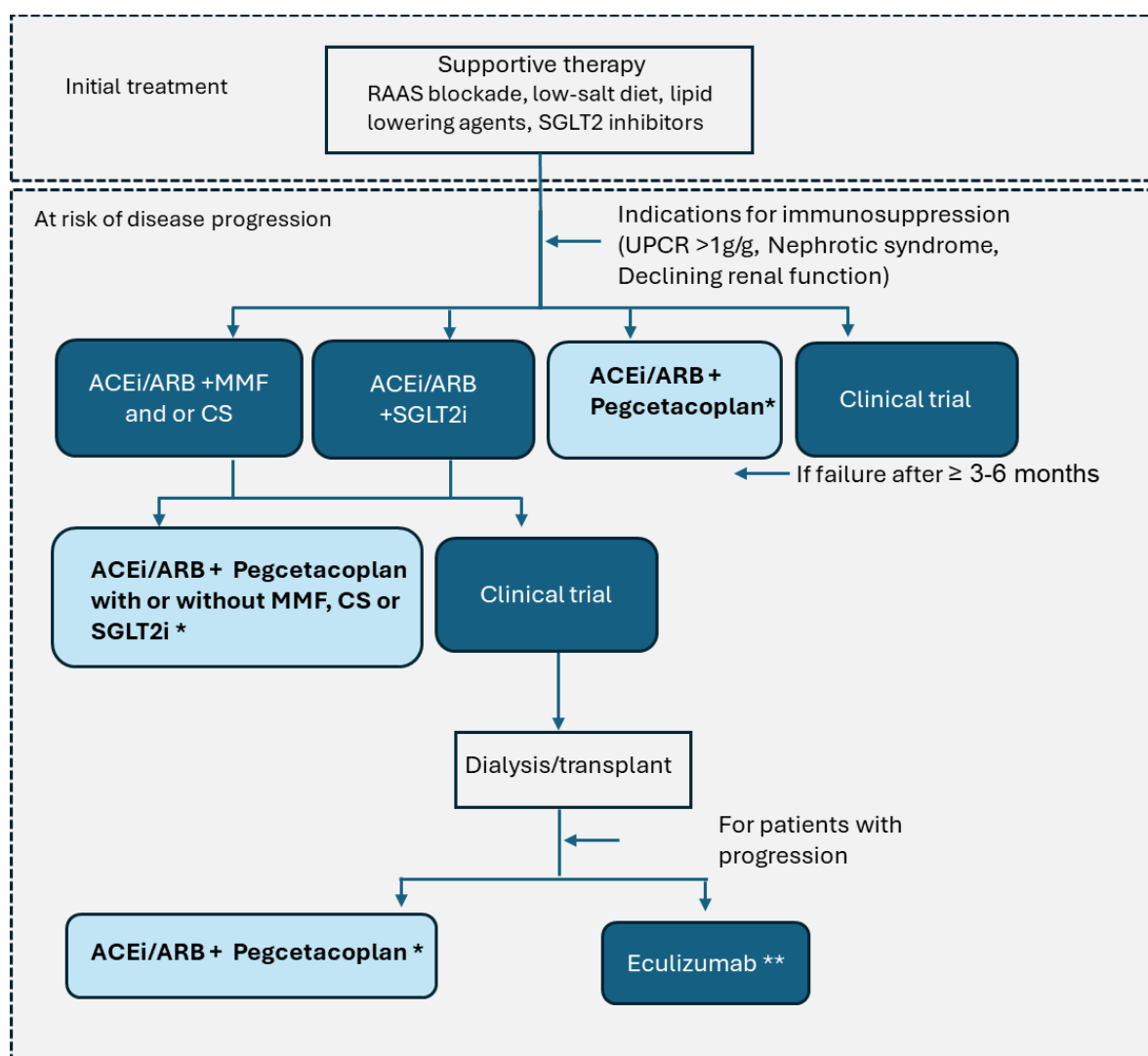
Pegcetacoplan action is independent of the presence of C3 or C5 nephritic factors (NeFs): *In vitro* studies demonstrate that pegcetacoplan blocks C3 and C5 convertases in the presence of C3 and C5 NeFs and therefore may also block complement overactivation in patients with these autoantibodies. (82)

C3 and C3b inhibition is a promising and potentially clinically effective approach for the treatment of C3G and primary IC-MPGN, a broader effect in most patient is expected when blocking C3, the central component of all complement pathways. An initial and rapid reduction in proteinuria is expected as inflammation is reduced, followed by a slower and further decline in proteinuria as C3 fragments are removed and the glomerular structure is restored. As supported by the trial data, (see section) improvements in both proteinuria and GFR have been demonstrated, which are expected to result in prolonged renal survival. Therefore, treatment with pegcetacoplan is expected to interrupt the process in C3G/primary IC-MPGN that leads to both proteinuria and ESKD.

Based on the pathophysiology of the disease, and the mechanism of action of pegcetacoplan, a reduction in proteinuria can serve as a non-invasive marker of disease improvement, and is strongly associated with reduced risk of kidney failure (83) (Sobi, data on file) (40), (41)

The proposed positioning of pegcetacoplan is outlined in Figure 4.

Figure 4. Proposed positioning of pegcetacoplan in C3G and primary IC-MPGN



Adapted from KDIGO guidelines for glomerular disease (9) and a KDIGO international consensus meeting on C3G. (84). * Pegcetacoplan would be offered alongside an ACEi or ARB. Clinical statements indicate that pegcetacoplan may displace MMF and CS. Furthermore, a post-hoc analysis of VALIANT (85) showed that efficacy was comparable in those patients on or not on concomitant immunosuppression **Eculizumab is used off-label, and in the UK, it is only available for C3G patients who have undergone a transplant, with limited evidence of its effectiveness in the native [ESUOM49] (66) and transplanted kidney [ESUOM44] (67). SGLT2 inhibitors are only recommended in the adult population with CKD [TA942] (86), [TA775] (87). Supportive therapy is usually continued after 1st line (9).

Abbreviations: MMF, mycophenolate mofetil; UPCR, urine protein/creatinine ratio; RAAS, renin angiotensin system; SGLT-2, sodium-glucose co-transporter-2

There is no specific data to support stopping treatment with pegcetacoplan based on efficacy. However, the recent advisory board of UK clinical experts (Sobi, d.o.f) (40)

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proposed that patients who reached a $<1\text{g/g}$ UPCR might stop treatment, based on efficacy. This was further supported by the majority view in additional interviews conducted by Sobi, (d.o.f) (40) who stated that it would be reasonable to stop treatment in responders, with the option to restart in the event of relapse. Advisors also recommended that treatment could stop when dialysis was necessary, due to lack of efficacy . (88).

Pegcetacoplan would be prescribed in secondary care with routine follow-up in secondary care.

1.4 Equality considerations

Sobi does not believe there are equality considerations that would be likely to impact the recommendations and their appropriateness. However, the committee should consider whether the longer waiting times faced by Black and Asian people represents a health inequality. This aligns with comments made during the scoping consultation for iptacopan, in which the National Kidney Federation said, “It should be kept in mind that there are longer waiting time for kidney transplants for Black and Asian patients compared to White. A third of people (35 %) waiting for a kidney across the UK are from minority ethnic groups but in 2017/18, of those providing their ethnicity when registering on the NHS Organ Donor Register, only 3.3 % were Asian, 1 % were black and 2 % were mixed race. This may need to be factored in when considering who should be treated and when, to ensure all patients have the best chance”.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical trial evidence associated with the decision problem outlined in Section 1.1. See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to pegcetacoplan in C3G and primary IC-MPGN.

2.2 List of relevant clinical effectiveness evidence

In summary, a total of 26 publications consisting of 7 unique trials were identified by the SLR, extracted and assessed for methodological quality. Due to the rare nature of the disease, the SLR was designed to capture trials assessing any intervention for these patients. Of the 7 unique trials identified, 3 studies presented evidence for pegcetacoplan:

- NOBLE (NCT04572854) was a multinational, prospective phase 2 RCT investigating the efficacy and safety of 12 weeks of pegcetacoplan (n = 10) or standard of care (SOC; n = 3) in 13 adult patients with recurrent C3G (n = 10) or IC-MPGN (n = 3) after kidney transplant. Its findings have been reported in a peer-reviewed journal article (89) as well as 5 congress materials, (90-93) including *post-hoc* analyses of patient-level data (91) and patient evolution through to 52 weeks that included a 40 week pegcetacoplan open-label treatment period after the initial comparative 12-week period (92).
- DISCOVERY (NCT03453619) (79) was a single-arm, open-label, phase 2 study in adolescents and adults with native C3G receiving pegcetacoplan (n = 8) for 48 weeks
- VALIANT (NCT05067127) was a multinational, phase 3 RCT evaluating the efficacy and safety of 26 weeks of pegcetacoplan (n = 63) versus placebo (n = 61) in 124 adult and adolescent patients with native and recurrent C3G or IC-MPGN, followed by a 26-week open-label pegcetacoplan treatment period. (85, 94-100). The study is reported in 8 congress materials, including posters, presentations and abstracts. The reports include efficacy and safety analysis of up to 52 weeks, (94) subgroup analyses of the adolescent population (96, 99) and patients with disease recurrence, (98) as well as *post hoc* analyses of patients with

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nephrotic range proteinuria (100) and concomitant immunosuppression.
(85)

As well as the two phase 2 studies and one phase 3 study, the efficacy and safety of pegcetacoplan in C3G and primary IC-MPGN has also been demonstrated through a single, long-term extension study (VALE/NCT05809531) associated with VALIANT. VALE was captured in the update to the SLR (101), but was excluded as outcomes were not reported.

Table 3 summarises the pivotal VALIANT trial, which is the primary evidence source informing the economic model.

Table 3. Clinical effectiveness evidence

Study	VALIANT (NCT05809531)
Study design	Phase 3, randomised, placebo-controlled, double-blinded efficacy and safety trial
Population	C3 Glomerulopathy (C3G) or primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)
Intervention(s)	Pegcetacoplan was administered subcutaneously b.i.w. - Adults of any weight and adolescents weighing ≥ 50kg: 1080 mg (20mL) - Adolescents weighing 35 to < 50kg, 1st dose is 648 mg (12 mL), 2nd dose is 810 mg (15 mL), and maintenance dose is 810 mg (15 mL): - Adolescents weighing 30 to < 35kg, 1st and 2nd doses are 540mg (10mL) and maintenance dose is 648 mg (12 mL)
Comparator(s)	Placebo (matching volumes) ^a
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	n/a
Reported outcomes specified in the decision problem	Proteinuria reduction Stabilisation of deterioration in eGFR Mortality Adverse effect of treatment HRQoL

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Study	VALIANT (NCT05809531)
All other reported outcomes	Reduction in C3c staining C3G histologic activity score index

a: Best supportive care was allowed to continue in both arms of the trial.

Table 4 summarises the long-term extension study, VALE/ NCT05809531. VALE was captured in the SLR (101) but was excluded as outcomes were not reported. VALE was not used to populate the economic model but is included in sections 3.2 to 3.6. This study was not included in the economic model because it is an ongoing trial, and the currently available interim data does not supplement the pivotal trial data sufficiently to be included in the economic model. However, the results of this study support the clinical impact of pegcetacoplan on proteinuria reduction and stabilisation of the decline in eGFR, both of which are important clinical endpoints and key drivers of the economic model. VALE has therefore been included as a source of clinical effectiveness data.

Table 4. Clinical effectiveness evidence

Study	VALE/NCT05809531
Study design	Phase 3, open-label, single-arm, nonrandomised long-term extension efficacy and safety study
Population	C3 Glomerulopathy (C3G) or primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)
Intervention(s)	Pegcetacoplan was administered subcutaneously b.i.w. - Adults of any weight and adolescents weighing ≥ 50kg: 1080 mg (20mL) - Adolescents weighing 35 to <50kg, 1st dose is 648 mg (12 mL), 2nd dose is 810 mg (15 mL), and maintenance dose is 810 mg (15 mL): - Adolescents weighing 30 to <35kg, 1st and 2nd doses are 540mg (10mL) and maintenance dose is 648 mg (12 mL)
Comparator(s)	n/a
Indicate if study supports application for marketing authorisation	Interim data was submitted to the EMA to provide additional supportive evidence for the long-term treatment effects of pegcetacoplan on proteinuria and renal function in patients with C3G and primary IC-MPGN.
Indicate if study used in the economic model	No
Rationale if study not used in model	The VALE study is ongoing and therefore finalised data is not available for incorporation into the economic model. However, interim results are available to support the effect of pegcetacoplan on outcomes within the scope of the

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Study	VALE/NCT05809531
	decision problem, and is therefore summarised in the clinical sections of this submission.
Reported outcomes specified in the decision problem	Proteinuria reduction Stabilisation of deterioration in eGFR Mortality Adverse effect of treatment HRQoL
All other reported outcomes	Normalisation of serum C3

Table 5 and Table 6 summarise the NOBLE and DISCOVERY trials, respectively. Neither study was used to populate the economic model because they had low sample sizes and differed appropriately from the pivotal VALIANT trials, limiting the appropriateness of pooling outcomes for implementation into the model. However, the results of both studies support the clinical impact of pegcetacoplan on proteinuria reduction and stabilisation of the decline in eGFR, both of which are key drivers of the economic model. Therefore, details of these phase II studies have been included in Appendix J: Supporting clinical effectiveness evidence from phase II trials. Evidence for NOBLE is taken from Bomback et. al. 2025 (89) (week 12 data) and the clinical study report (week 52 data) (102), whilst evidence for DISCOVERY is taken from Dixon 2023 (79).

Table 5. Clinical effectiveness evidence

Study	NOBLE (NCT04572854)
Study design	Phase 2, open-label, randomised, controlled efficacy and safety trial
Population	Adult Patients with posttransplant recurrence of C3 Glomerulopathy (C3G) or primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)
Intervention(s)	1080mg of pegcetacoplan was administered subcutaneously twice weekly for the duration of the main study period from weeks 1 to 52. Biopsies occurred on weeks 12 and 52.
Comparator(s)	No treatment with pegcetacoplan was given during the randomised controlled portion of the study (Weeks 1 to 12). After week 12, subjects received 1080mg of pegcetacoplan subcutaneously twice weekly for the remainder of the trial until week 52. Biopsies occurred on week 52.

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Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale if study not used in model	The trial had a small sample size and short duration of randomised controlled trial period (12 weeks), therefore results are less appropriate for inclusion than the VALIANT data. In addition, there were differing inclusion criteria in terms of eGFR levels and age requirements, meaning it may not be appropriate to pool the outcome data with that collected in VALIANT.
Reported outcomes specified in the decision problem	Stabilisation or changes in eGFR Changes in proteinuria Adverse effect of treatment
All other reported outcomes	Changes in C3c staining over time. Stabilisation or changes in serum creatinine concentration

Table 6. Clinical effectiveness evidence

Study	DISCOVERY (NCT03453619)
Study design	Phase 2, single arm, open-label, randomised efficacy and safety trial
Population	Adult patients with complement-mediated glomerulopathies
Intervention(s)	360mg of pegcetacoplan was administered subcutaneously, daily from weeks 1 to 24, then 1080 mg twice weekly up to 48 weeks.
Comparator(s)	No pegcetacoplan treatment from weeks 1 to 12, followed by 1080mg of pegcetacoplan administered subcutaneously twice weekly from weeks 13 to 53.
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	No

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Rationale if study not used in model	The study only included a small sample of patients with C3G (n=7) and was not randomised. It would therefore not be appropriate to pool the outcomes from this trial with those of the pivotal VALIANT study.
Reported outcomes specified in the decision problem	Change from baseline in proteinuria Stabilisation or improvement in eGFR Adverse effect of treatment
All other reported outcomes	Changes in serum/plasma disease biomarkers

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Methodology

2.3.1.1 VALIANT trial design

VALIANT is a pivotal phase 3, randomised, placebo-controlled, double-blinded, multicentre study to evaluate the efficacy and safety of twice-weekly SC infusions of pegcetacoplan in patients diagnosed with C3G or primary IC-MPGN.

The planned duration of participation in the study for each participant was a maximum of approximately 70 weeks. The study consisted of 4 parts:

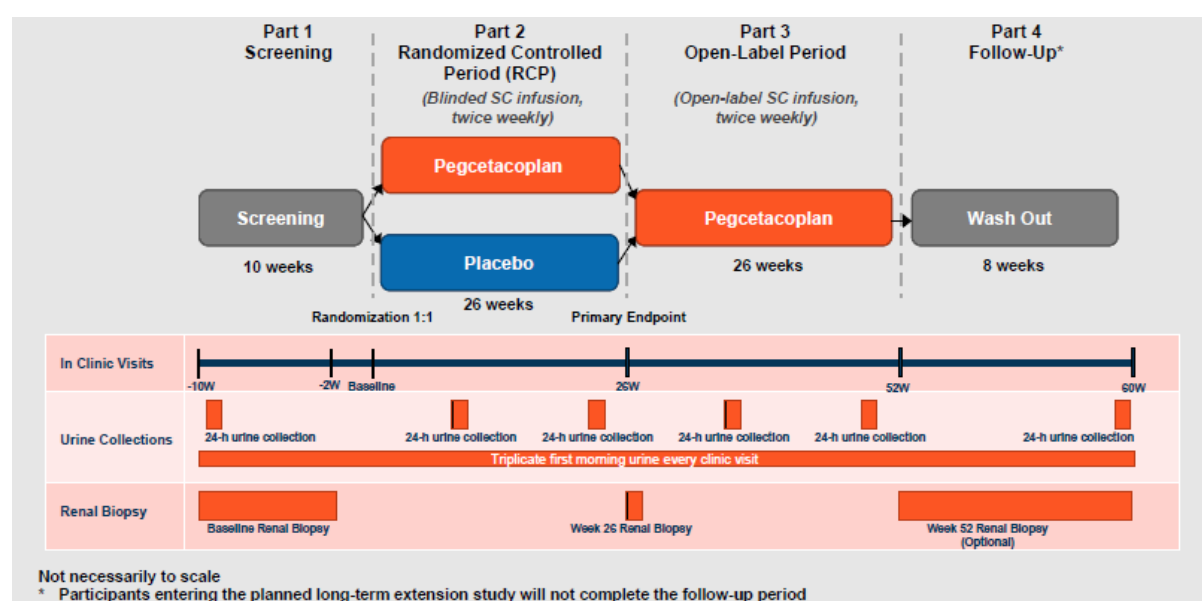
- Part 1: 10-week screening period
- Part 2: 26-week randomised controlled period (RCP)
- Part 3: 26-week open-label period (OLP)
- Part 4: 8-week follow-up period (only for participants who do not roll into a long-term extension study)

The trial started in November 2021 and the first participant in the trial was enrolled on May 30th, 2022. The last participant completed on 14th January 2025. The latest data cutoff was 12th February 2025.

A schematic of the overall study design is shown in Figure 5.

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Figure 5. VALIANT study design schematic



Abbreviations: SC, subcutaneous; UPCR, urine protein-to-creatinine ratio; W, week.

Participants were randomly assigned 1:1, via a computer-generated randomization schedule, to either the pegcetacoplan group (pegcetacoplan treatment throughout the RCP and open-label period) or the placebo group (placebo treatment during the RCP and pegcetacoplan treatment during the open-label period). To achieve balance between the arms, 2 stratification factors were applied to the randomization. The first stratification factor examined participants with post-transplant recurrence versus non-transplant participants. This was followed by the second stratification factor, which examined participants with baseline renal biopsies (either collected during screening or a historic biopsy collected within 28 weeks prior to randomization) versus participants without baseline renal biopsies.

At the end of the RCP, a renal biopsy was required for participants aged 18 years and older to advance to the OLP. This was not required for participants younger than 18 years who could have advanced to the OLP upon completion of all assessments for weeks 24 through 26, other than the renal biopsy.

At the end of the RCP, participants from both groups proceeded to the 26-week OLP, in which all participants were treated with pegcetacoplan twice weekly. Open-label dosing began at the first visit after the week 26 renal biopsy for adults and any Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

adolescents providing renal biopsies. Open-label dosing for adolescents not providing renal biopsies started at the week 26 visit. At the end of the OLP, there was an optional renal biopsy. Participants younger than 18 years who did not have a baseline biopsy within 28 weeks of day 1 did not have a biopsy at the end of the OLP. Upon completion of the OLP, participants entered the 8-week follow-up period (part 4) unless they entered a long-term extension study (Study APL2-C3G-314/VALE/ NCT05809531). An estimated 100 participants (of the 120 enrolled in VALIANT), who in the opinion of the investigator had experienced clinical benefit from pegcetacoplan, were invited to participate in the long-term extension study (APL2-C3G-314/VALE).

Study sites

Patients were enrolled at 122 sites across 19 countries: Argentina (3 sites), Australia (4 sites), Austria (2 sites), Belgium (4 sites), Brazil (14 sites), Canada (2 sites), Czechia (2 sites), France (11 sites), Germany (6 sites), Israel (2 sites), Italy (10 sites), Japan (8 sites), Netherlands (3 sites), Poland (2 sites), South Korea (4 sites), Spain (8 sites), Switzerland (3 sites), UK (9 sites), and US (25 sites).

Study eligibility criteria

The key inclusion and exclusion criteria for VALIANT are described in Table 7.

Table 7. Key eligibility criteria for VALIANT

Inclusion	Exclusion
Aged at least 18 years; where approved, adolescents (aged 12-17 years) weighing at least 30 kg may also be enrolled.	Previous exposure to pegcetacoplan
A diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant)	Evidence of improving renal disease in the 8 weeks prior to screening or during the screening period according to available data; improving renal disease is defined as >30% increase in eGFR or >50% decrease in proteinuria.
Evidence of active renal disease, based on one or more of the following: 1. In adults or adolescents with a baseline renal biopsy (either one collected during screening or a historic biopsy collected within 28 weeks prior to randomisation), at least 2+ C3c staining on the baseline renal biopsy 2. In adolescents not providing a baseline renal biopsy, at least one of the following: • Plasma sC5b-9 level above the upper limit of normal during screening • Serum C3 below the lower limit of normal (LLN) during screening • Presence of an active urine sediment during screening, as evidenced by hematuria with at least 5 red blood cells per high-power field and/or red blood cell casts on routine local or central microscopic analysis of urine • Presence of C3 nephritic factor within 6 months of screening, based on central laboratory results or medical history	From a renal transplant participant, evidence of rejection that requires treatment in the baseline renal biopsy collected during screening
No more than 50% global glomerulosclerosis or interstitial fibrosis on the baseline biopsy for adult participants or adolescent participants providing a baseline biopsy	C3G/IC-MPGN secondary to another condition (e.g., infection, malignancy, monoclonal gammopathy, a systemic autoimmune disease such as systemic lupus erythematosus, chronic antibody-mediated rejection, or a medication), in the opinion of the investigator
At least 1 g/day of proteinuria on a screening 24-hour urine collection and a UPCR of at least 1000 mg/g in at least 2 FMU samples collected during screening	Current or prior diagnosis of HIV, hepatitis B, or hepatitis C infection or positive serology during screening that is indicative of infection with any of these viruses
eGFR ≥ 30 mL/min/1.73 m ² calculated by the CKD-EPI creatinine equation for adults or the Bedside Schwartz equation for adolescents	Body weight greater than 100 kg at screening
Stable regimen for C3G/IC-MPGN treatment, as described below:	Hypersensitivity to pegcetacoplan or to any of the excipients

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• Angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and/or sodium-glucose cotransporter-2 inhibitor (SGLT-2) therapy that is stable and optimized, in the opinion of the investigator, for at least 12 weeks prior to randomisation • Stable doses of other medications that can affect proteinuria (e.g., steroids, mycophenolate mofetil, and/or other allowed immunosuppressants that the participant is receiving for treatment of C3G or IC-MPGN) for at least 12 weeks prior to randomisation • If a participant is on prednisone (or other systemic corticosteroid) for C3G or IC-MPGN treatment, the dosage is stable and no higher than 20 mg/day (or equivalent dosage of a corticosteroid other than prednisone) for at least 12 weeks prior to randomisation	
Have received vaccinations against <i>S pneumoniae</i> , <i>N meningitidis</i> (types A, C, W, Y, and B), and H influenzae (type B) as per ACIP recommendations for adults or children with complement deficiencies. Vaccination series should be initiated at least 14 days prior to randomisation. Vaccination is mandatory unless documented evidence exists that participants are non-responders to vaccination	History of meningococcal disease
	Malignancy, except for the following: • Cured basal or squamous cell skin cancer • Curatively treated in situ disease • Malignancy-free and off treatment for ≥ 5 years
	Severe infection (e.g., requiring IV antibiotic therapy) within 14 days prior to the first dose of Pegcetacoplan
	An absolute neutrophil count < 1000 cells/mm ³ at screening
	Significant other renal disease that would, in the opinion of the investigator, confound interpretation of study results.
	Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or 5 half-lives from the last dose of investigational agent (whichever is longer) prior to screening period
	Use of rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan within 5 half-lives of that product prior to the screening period.

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All participants received SC infusions of pegcetacoplan or matching volumes of placebo twice weekly in addition to any pre-existing standard of care (SoC). The dosing regimens for pegcetacoplan and the matching volume of placebo are presented in Table 8.

Table 8. Planned dosing regimen (pegcetacoplan and placebo)

Weight	First dose (infusion volume)	Second dose (infusion volume)	Maintenance dosing regimen (infusion volume)
All adult participants, adolescent participants ≥50 kg	1080 mg (20 mL)	1080 mg (20 mL)	1080 mg twice weekly (20 mL)
Adolescent participants 35 to <50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
Adolescent participants 30 to <35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

If a participant missed any regularly scheduled doses for any reason, all efforts were made to restart dosing as soon as possible to reach and maintain therapeutic steady-state concentrations of pegcetacoplan

Dosing was blinded in the RCP; the OLP was not blinded. All central evaluations (including evaluation of renal biopsies by the central pathologist) were blinded to treatment assignment. Participants, the sponsor, investigators, and all study site personnel conducting study-related activities (including carrying out study procedures, evaluating participants, and entering and/or evaluating study data) remained blinded to treatment allocations during the RCP at least until all participants had completed the week 26 assessments and the RCP portion of the database had been locked. Although treatment in the OLP was not blinded, investigators, study site personnel, and participants remained blinded to the RCP treatment assignment.

Concomitant medications

Permitted medications included stable doses of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and/or SGLT-2 inhibitors. Additionally, stable doses of other medications that could affect proteinuria, including steroids, mycophenolate mofetil (MMF), and/or other allowed immunosuppressants that the participant is receiving for treatment of C3G or primary IC-MPGN.

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Prohibited medications: rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan (including, but not limited to, eculizumab and/or ravulizumab) was prohibited within 5 half-lives of that product prior to screening and for the duration of the study.

In the event of an increase in serum creatinine to at least 2 times the baseline level that in the opinion of the investigator was due to the underlying C3G/IC-MPGN disease, rescue therapy could be considered, such as high-dose corticosteroids and/or C5 inhibitor treatment.

Outcomes

The primary objective of VALIANT was to assess the efficacy of twice-weekly SC doses of pegcetacoplan compared with that of placebo in patients with primary C3G or IC-MPGN on the basis of a reduction in proteinuria.

Secondary objectives:

- To assess the effect of pegcetacoplan on eGFR
- To assess the effect of pegcetacoplan on additional C3G/primary IC-MPGN disease-related parameters
- To evaluate the safety of pegcetacoplan over 52 weeks of treatment

2.3.1.2 VALE trial design

VALE is a phase 3, open-label, single arm, multicentre study to evaluate the long-term safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients with C3G or primary IC-MPGN who have completed participation in study NCT05809531/ VALIANT and who, in the opinion of the investigator, had experienced clinical benefit from pegcetacoplan administration. Participants are enrolled in this study for a minimum of 120 weeks (approximately 2.5 years) and may continue to receive treatment with pegcetacoplan until it is commercially available for treatment of C3G and/or primary IC-MPGN or the development program for C3G and/or primary IC-MPGN is terminated. If eligible to participate, participants can enter this study as soon as their 52-week treatment period in VALIANT has ended;

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completion of the 8-week follow-up period described in the VALIANT protocol is not required. Participants will be evaluated every 12 weeks for the duration of this study. Safety and efficacy will be monitored at each visit.

After completion of the study treatment period, participants entered the follow-up period or completed a transition visit, depending on whether they would continue to receive commercially available or alternately sourced pegcetacoplan. Participants who discontinued pegcetacoplan treatment entered the follow-up period and returned for an exit visit 8 weeks after their last dose of pegcetacoplan. Participants who transition to commercially available or alternately sourced pegcetacoplan completed the transition visit. Participants were to complete either the follow-up period or the transition visit, but not both.

The trial started in May 2023 with the first participant enrolled 29th May 2023. The latest data cutoff was 20th June 2024. The trial is ongoing. At data cutoff (20th June, 2024) 53 participants were enrolled in the study.

Study sites

44 sites were participating in this study as of the interim analysis across 15 countries: Argentina (1 site), Australia (2 sites), Belgium (1 site), Brazil (8 sites), Czechia (1 site), France (2 sites), Israel (1 site), Italy (3 sites), Japan (2 sites), Netherlands (3 sites), South Korea (3 sites), Spain (3 sites), Switzerland (1 site), UK (2 sites), and US (11 sites).

Study eligibility criteria

The key inclusion and exclusion criteria for VALE are described in Table 9.

Table 9. Key eligibility criteria for VALE

Inclusion	Exclusion
Participants must have completed participation in Study APL2-C3G-310/VALIANT through the week 52 visit requirements.	Any condition that, in the opinion of the investigator, creates an undue risk for the participant by participating in the study or is likely to confound interpretation of the study results
Participants must have experienced clinical benefit from pegcetacoplan while participating in the previous study, in the opinion of the investigator	Female participants who are or are planning to become pregnant or who are currently breastfeeding and are unwilling to discontinue for the duration of the study and for at least 90 days after the final dose of study drug
Participants must remain on a stable regimen for C3G or primary IC-MPGN treatment according to the requirements of VALIANT.	Any condition that, in the opinion of the investigator, creates an undue risk for the participant by participating in the study or is likely to confound interpretation of the study results
Participants must have received vaccinations against S. pneumoniae, N. meningitidis (types A, C, W, Y, and B), and H. influenzae (type B) according to the requirements of the VALIANT study and agree to receive any additional vaccinations recommended according to Advisory Committee on Immunization Practices recommendations for adults or children with complement deficiencies and/or immunocompromising conditions or other similar local applicable guidelines	

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All participants received SC infusions of pegcetacoplan twice weekly, which was started in the VALIANT study. The dosing regimens for pegcetacoplan in this study matched the maintenance dosing regimen from VALIANT as presented in Table 8.

Concomitant medications

In the event of an increase in serum creatinine to at least 2 times the baseline level that in the opinion of the investigator was due to the underlying C3G or primary IC-MPGN disease, rescue therapy could be considered, such as high-dose corticosteroids, C5 inhibitor treatment, or both.

If rescue therapy was instituted, the participant was considered a non-responder for the analysis of any efficacy endpoints based on the proportion of participants meeting a specified criterion. If a participant received rescue therapy that was not a prohibited concomitant medication, they were allowed to remain on study drug, although that participant was deemed a non-responder for the analysis of any efficacy endpoints based on the proportion of participants meeting a specified criterion. If a participant received rescue therapy that was a prohibited concomitant medication, that participant was discontinued from the study and deemed a non-responder.

The use of rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan (including but not limited to eculizumab and/or ravulizumab) was prohibited for the duration of the study.

Outcomes

Primary efficacy outcome is the proportion of participants with a reduction in proteinuria over time compared to the pretreatment value.

Key secondary outcomes include:

- The proportion of participants with eGFR values that are stable or improved from pretreatment values over time
- The proportion of participants with normalisation of serum albumin and serum C3 levels over time
- FACIT fatigue score

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- Time to progression to a composite clinical outcome (at least one of the following: sustained doubling of serum creatinine, progression to chronic kidney disease stage 5 or end-stage renal disease, renal transplantation, or death from renal or cardiovascular disease).

Safety outcomes including:

- Treatment emergent adverse events (TEAEs)
- The number and incidence of rejection episodes (for posttransplant participants only)
- The number and incidence of graft loss (for posttransplant participants only)
- The incidence of death, stratified by transplant history and overall

2.3.2 Comparative summary of trial methodology

A comparative summary of trial methodology for the VALIANT and VALE trials is presented in Table 10.

Table 10. Comparative summary of trial methodology

Trial number (acronym)	NCT05809531 (VALIANT)	NCT05809531 (VALE)
Location	122 centres globally, including North and South America, Europe and Asia Pacific region	44 sites globally, including North and South America, Europe and Asia Pacific region
Trial design	Phase 3 randomised, double-blinded, placebo-controlled study	Phase 3 non-randomised, open-label, single group long term extension study
Eligibility criteria for participants	People aged at least 18 years; where approved, adolescents (aged 12-17 years and weighing at least 30 kg) with a diagnosis of primary C3G or primary IC-MPGN (with or without previous renal transplant)	Participants must have completed participation in VALIANT through the week 52 visit requirements and experienced clinical benefit from pegcetacoplan
Settings and locations where the data were collected	Argentina (3 sites), Australia (4 sites), Austria (2 sites), Belgium (4 sites), Brazil (14 sites), Canada (2 sites), Czechia (2 sites), France (11 sites), Germany (6 sites), Israel (2 sites), Italy (10 sites), Japan (8 sites), Netherlands (3 sites), Poland (2 sites), South Korea (4 sites), Spain (8 sites), Switzerland (3 sites), UK (9 sites), and US (25 sites).	Argentina (1 site), Australia (2 sites), Belgium (1 site), Brazil (8 sites), Czechia (1 site), France (2 sites), Israel (1 site), Italy (3 sites), Japan (2 sites), Netherlands (3 sites), South Korea (3 sites), Spain (3 sites), Switzerland (1 site), UK (2 sites), and US (11 sites)
Trial drugs	Participants were randomly assigned in a 1:1 ratio to receive either SC pegcetacoplan (n = 63; 1080 mg for adults or adolescents >50 kg and weight-based dosing for adolescents <50 kg) or SC placebo (n=61) twice weekly, in addition to any pre-existing SoC for the 26-week RCP. For the OLP, all participants received pegcetacoplan (at the above dose) in addition to any pre-existing SoC.	Participants received SC pegcetacoplan (as per data cut-off [20 June 2024] n=53; 1080 mg for adults or adolescents >50 kg and weight-based dosing for adolescents <50 kg), in addition to any preexisting SoC.
Permitted and disallowed concomitant medication	Permitted medications: ACE inhibitors, ARBs, SGLT-2 inhibitors, steroids, MMF Prohibited medications: rituximab, belimumab	Permitted medications: ACE inhibitors, ARBs, SGLT-2 inhibitors, steroids, MMF Prohibited medications: rituximab, belimumab .

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Primary outcomes (including scoring methods and timings of assessments)	The log-transformed ratio of UPCR at Week 26 compared to baseline	The log-transformed ratio of urine protein-to-creatinine ratio (UPCR) over time compared to pretreatment baseline.
Other outcomes used in the economic model/specified in the scope	• Stabilisation of deterioration in eGFR • HRQoL • Adverse effects of treatment • Mortality	• Stabilisation of deterioration in eGFR • HRQoL • Time to progression to a composite clinical outcome (at least one of the following: sustained doubling of serum creatinine, progression to chronic kidney disease stage 5 or end-stage renal disease, renal transplantation, or death from renal or cardiovascular disease) • Adverse effects of treatment • Mortality
Pre-planned subgroups	Subgroup analyses were conditioned for age group, sex, race, geographic location, disease type, transplant history, baseline FMU UPCR: <3000 mg/g, ≥3000 mg/g, baseline eGFR: <60 mL/min/1.73 m ² , ≥60 mL/min/1.73 m ² , baseline C3 level: normal, below the LLN, Baseline immunosuppressants use: yes, no (based on ATC level 2 of "IMMUNOSUPPRESSANTS" and/or "CORTICOSTEROIDS FOR SYSTEMIC USE")	Disease type and transplant status

2.3.3 Trial baseline characteristics

2.3.3.1 VALIANT baseline characteristics

Demographic characteristics

The demographic characteristics of patients in the Intention-to-treat (ITT) population are summarized in Table 11. Overall, patient characteristics at baseline were generally similar and balanced between treatment groups.

The age difference between treatment groups was not considered to be meaningful as data demonstrated similar results between adolescents and adults.

Overall, 54 participants (43.5%) were male, and 70 participants (56.5%) were female. Most participants were White (73.4%) and identified as Not Hispanic or Latino (71.0%). The mean weight, height, body mass index, systolic blood pressure, and diastolic blood pressure at baseline were balanced between the pegcetacoplan and placebo groups.

Table 11. Baseline demographics (ITT set)

	Pegcetacoplan (N =63) n (%)	Placebo (N = 61) n (%)	Overall (N = 124) n (%)
Age at screening (years), n	63	61	124
Mean (SD)	28.2 (17.1)	23.6 (14.3)	26.0 (15.9)
Median	19.0	19.0	19.0
Q1, Q3	15.0, 45.0	16.0, 26.0	15.0, 27.0
Min, max	12, 62	12, 74	12, 74
Age group: adolescent (12-17 years), n (%)	28 (44.4)	27 (44.3)	55 (44.4)
Age group: adult (≥18 years), n (%)	35 (55.6)	34 (55.7)	69 (55.6)
Sex, n (%)			
Male	26 (41.3)	28 (45.9)	54 (43.5)
Female	37 (58.7)	33 (54.1)	70 (56.5)
Race, n (%)			
White	45 (71.4)	46 (75.4)	91 (73.4)
Asian	9 (14.3)	9 (14.8)	18 (14.5)
Black or African American	1 (1.6)	0	1 (0.8)
American Indian or Alaskan Native	1 (1.6)	0	1 (0.8)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	7 (11.1)	6 (9.8)	13 (10.5)

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Ethnicity, n (%)			
Hispanic	15 (23.8)	10 (16.4)	25 (20.2)
Not Hispanic or Latino	41 (65.1)	47 (77.0)	88 (71.0)
Not reported ^a	6 (9.5)	2 (3.3)	8 (6.5)
Unknown	1 (1.6)	2 (3.3)	3 (2.4)

Abbreviation: ITT, intent-to-treat. ^a Some participants with ethnicity not reported because some countries do not allow the collection of ethnicities.

Disease characteristics

Baseline disease characteristics for the ITT set are summarised in Table 12. Of the 124 participants overall, 51 (81.0%) in the pegcetacoplan group, and 45 (73.8%) in the placebo group had C3G underlying disease based on screening biopsy. Twelve (19.0%) participants in the pegcetacoplan group and 16 (26.2%) in the placebo group had IC-MPGN underlying disease, based on screening biopsy. Medical history characteristics were balanced. Collection of medical history data showed that participants in the placebo group had more genetic risk factors for C3G/IC-MPGN (16.4%) than participants in the pegcetacoplan group (6.3%). Because genetic testing was not a requirement for this study, this numerical difference may result from the fact that not all participants had the genetic test. Mean (SD) baseline proteinuria assessments (measured by 24-hour collection and triplicate FMU) were slightly higher in the pegcetacoplan group (baseline 24-hour UPCR: 3954.7mg/g (2887.6); baseline triplicate FMU: 3123.8 mg/g (2408.3)) than in the placebo group (baseline 24-hour UPCR:3290.1 (2357.5); baseline triplicate FMU: 2540.8 (2014.6)). Mean (SD) baseline eGFR was slightly lower in the pegcetacoplan group (78.5 [34.1] mL/min/1.73 m²) than the placebo group (87.3 [37.1] mL/min/1.73 m²). Differences in baseline characteristics between treatment groups were not considered to be meaningful enough to have any impact on study outcomes.

Table 12. Key baseline disease characteristics (ITT set)

	Pegcetacoplan (N = 63)	Placebo (N = 61)	Overall (N = 124)
Underlying disease based on screening biopsy, n (%)			
C3G	51 (81.0)	45 (73.8)	96 (77.4)
C3GN	45 (71.4)	41 (67.2)	86 (69.4)
DDD	4 (6.3)	4 (6.6)	8 (6.5)
Undetermined	2 (3.2)	0	2 (1.6)
IC-MPGN	12 (19.0)	16 (26.2)	28 (22.6)

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Indication per disease specific medical history form, n (%)			
C3G	47 (74.6)	48 (78.7)	95 (76.6)
C3GN	43 (68.3)	43 (70.5)	86 (69.4)
DDD	4 (6.3)	4 (6.6)	8 (6.5)
Undetermined	0	1 (1.6)	1 (0.8)
IC-MPGN	16 (25.4)	13 (21.3)	29 (23.4)
Potential risk factors for C3G/IC-MPGN, n (%)			
Genetic risk factors	4 (6.3)	10 (16.4)	14 (11.3)
Autoantibodies	12 (19.0)	9 (14.8)	21 (16.9)
Other	8 (12.7)	8 (13.1)	16 (12.9)
Disease manifestations, n (%)			
Oedema	45 (71.4)	32 (52.5)	77 (62.1)
Fatigue	16 (25.4)	8 (13.1)	24 (19.4)
Haematuria	37 (58.7)	39 (63.9)	76 (61.3)
High blood pressure	35 (55.6)	29 (47.5)	64 (51.6)
Hyperlipidaemia	24 (38.1)	19 (31.1)	43 (34.7)
Nephrotic syndrome	32 (50.8)	27 (44.3)	59 (47.6)
Proteinuria	58 (92.1)	55 (90.2)	113 (91.1)
Reduced GFR	21 (33.3)	14 (23.0)	35 (28.2)
Baseline 24h UPCR (mg/g), n	63	61	124
Mean (SD)	3954.7 (2887.6)	3290.1 (2357.5)	3627.8 (2650.6)
Median	3151.0	2450.0	2861.0
Q1, Q3	2019.0, 5164.0	1633.0, 4236.0	1822.0, 4774.5
Min, max	631.0, 14624.0	730.0, 14351.0	631.0, 14624.0
Baseline triplicate FMU UPCR (mg/g) ^a , n	63	61	124
Mean (SD)	3123.8 (2408.3)	2540.8 (2014.6)	2836.9 (2233.6)
Median	2389.2	1815.6	2031.3
Q1, Q3	1502.7, 3779.9	1156.4, 3009.6	1287.2, 3544.6
Min, max	713.6, 11418.0	783.4, 10439.0	713.6, 11418.0
Baseline eGFR (mL/min/1.73 m ²), n	63	61	124
Mean (SD)	78.5 (34.1)	87.3 (37.1)	82.8 (35.8)
Median	78.0	91.0	85.5
Q1, Q3	47.0, 106.0	52.0, 122.0	50.5, 110.5
Min, max	25, 161	24, 156	24, 161
Baseline serum creatinine (mg/dL), n	63	61	124
Mean (SD)	1.1 (0.6)	1.1 (0.7)	1.1 (0.6)
Median	0.99	0.8	0.9
Q1, Q3	0.7, 1.6	0.7, 1.3	0.7, 1.4
Min, max	0.5, 2.7	0.4, 3.0	0.4, 3.0
Baseline serum C3 (mg/dL), n	63	61	124
Mean (SD)	60.6 (45.7)	56.3 (35.6)	58.5 (40.9)
Median	60.0	60.0	60.0
Q1, Q3	15.0, 100.0	20.0, 80.0	15.0, 92.5

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Min, max	10.0, 160.0	10.0, 130.0	10.0, 160.0
Baseline serum albumin (g/dL), n	63	61	124
Mean (SD)	3.3 (0.6)	3.4 (0.7)	3.3 (0.6)
Median	3.35	3.4	3.4
Q1, Q3	2.9, 3.7	2.9, 3.9	2.9, 3.9
Min, max	1.8, 4.5	1.9, 4.6	1.8, 4.8

Abbreviations: C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; FMU, first-morning spot urine; GFR, glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; ITT, intent-to-treat; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation; UPCR, urine protein-to-creatinine ratio. ^a the baseline UPCR reported was the result of the average of up to 9 values collected.

Baseline characteristics by transplant history

Baseline characteristics by transplant history for the ITT set are summarised in Table 13 and more details can be found in Appendix C. Baseline disease characteristics for the post-transplant and nontransplant subgroups were generally similar to those reported for the overall ITT set. When stratifying by transplant status, the nontransplant population had higher mean and median UPCR from 24-hour urine and average FMU, and the posttransplant population had lower mean and median eGFR compared to the overall ITT set.

Table 13. Baseline disease characteristics of participants by transplant status (ITT Set)

	Nontransplant		Post-transplant	
	Pegcetacoplan (N=58)	Placebo (N=57)	Pegcetacoplan (N =5)	Placebo (N =4)
Years since diagnosis ^a , n				
Mean (SD)	3.8 (3.5)	3.9 (3.7)	1.4 (1.5)	1.4 (1.6)
Median	3.29	3.28	0.51	0.73
Min; max	0.34; 18.40	0.03; 18.63	0.35; 3.57	0.31; 3.77
Underlying disease based on screening biopsy, n(%)				
C3G	46 (79.3)	42 (73.7)	5 (100)	3 (75.0)
C3GN	42 (72.4)	38 (66.7)	3 (60.0)	3 (75.0)
DDD	2 (3.4)	4 (7.0)	2 (40.0)	0
Undetermined	2 (3.4)	0	0	0
IC-MPGN	12 (20.7)	15 (26.3)	0	1 (25.0)
Potential causes of C3G/IC-MPGN, n (%)				
Genetic risk factors	4 (6.9)	9 (15.8)	0	1 (25.0)
Autoantibodies	9 (15.5)	8 (14.0)	3 (60.0)	1 (25.0)

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Other	7 (12.1)	7 (12.3)	1 (20.0)	1 (25.0)
UPCR from 24-hour urine (mg/g), n				
Mean (SD)	4092.8 (2964.7)	3413.1 (2385.5)	2353.4 (716.0)	1537.2 (738.6)
Median	3264.0	2571.0	2301.0	1542.5
Min; max	631.0; 14,264.0	1035, 14,351.0	1401.0; 3299.0	730.0; 2334.0
Mean of triplicate FMU UPCR (mg/g) ^b , n				
Mean (SD)	3202.1 (2483.3)	2618.9 (2057.3)	2215.0 (951.4)	1426.4 (631.0)
Median	2393.4	1850.5	1845.0	1243.0
Min; max	713.6; 11,418.0	783.4; 10,439.0	1266.4; 3315.1	895.3; 2324.2
eGFR (mL/min/1.73 m ²),n				
Mean (SD)	80.1 (34.7)	90.6 (36.0)	59.8 (20.9)	39.5 (13.2)
Median	82.5	95.0	63.0	37.5
Min; max	25; 161	24;156	34; 81	27; 56
Serum creatinine (mg/dL), n				
Mean (SD)	1.1 (0.6)	1.0 (0.6)	1.4 (0.7)	2.1 (0.7)
Median	0.9	0.8	1.3	2.1
Min; max	0.45; 2.71	0.43; 2.77	0.73; 2.35	1.32; 3.01
Serum albumin (g/dL), n				
Mean (SD)	3.3 (0.6)	3.3 (0.7)	3.6 (0.3)	4.0 (0.6)
Median	3.2	3.3	3.5	3.9
Min; max	1.8; 4.6	1.9; 4.5	3.4; 4.0	3.5; 4.8
Time since last kidney transplant (years), n				
Mean (SD)	NA	NA	11.4 (6.7)	5.8 (6.4)
Median	NA	NA	11.3	3.3
Min; max	NA	NA	3.8; 19.1	1.5; 15.4
Total number of kidney transplants, n (%)				
1	NA	NA	4 (80)	4 (100)
2	NA	NA	1 (20)	0
Did participant receive prior dialysis?, n (%)				
Yes	1 (1.7)	0	3 (60.0)	3 (75.0)
No	57 (98.3)	57 (100)	2 (40.0)	1 (25.0)
Time since most recent posttransplant recurrence (years), n				
Mean (SD)	NA	NA	1.5 (1.5)	1.4 (1.6)
Median	NA	NA	0.5	0.7
Min; max	NA	NA	0.4; 3.6	0.3; 3.8

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Time from last kidney transplant to the most recent posttransplant recurrence (years), n				
Mean (SD)	NA	NA	9.9 (7.1)	4.4 (7.1)
Median	NA	NA	10.8	1.2
Min; max	NA	NA	2.3, 18.7	0.2, 15.0
Disease manifestations, n				
Oedema	42 (72.4)	30 (52.6)	3 (60.0)	2 (50.0)
Fatigue	16 (27.6)	8 (14.0)	0	0
Haematuria	34 (58.6)	37 (64.9)	3 (60.0)	2 (50.0)
High blood pressure	30 (51.7)	25 (43.9)	5 (100)	4 (100)
Hyperlipidaemia	22 (37.9)	18 (31.6)	2 (40.0)	1 (25.0)
Nephrotic syndrome	30 (51.7)	25 (43.9)	2 (40.0)	2 (50.0)
Proteinuria	53 (91.4)	51 (89.5)	5 (100)	4 (100)
Reduced GFR	17 (29.3)	11 (19.3)	4 (80.0)	3 (75.0)

Abbreviations: C3G, C3 glomerulonephritis; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; FMU, first-morning urine; GFR, glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; n, number of unique participants in statistic; N, number of participants in study group; NA, not applicable; UPCR, urine protein-to-creatinine ratio. ^a For posttransplant participants, the date of diagnosis refers to the most recent posttransplant recurrence (based on medical history). ^b The triplicate FMU UPCR reported was the result of the average of up to 9 values collected.

Baseline biopsy characteristics

All participants in both groups had at least 2+ C3c staining upon entering the study per the protocol requirement. Baseline biopsy characteristics were generally balanced between groups with the exception of glomerular crescents.

Glomerular crescents were absent for 61 participants (96.8%) in the pegcetacoplan group vs 55 participants (90.2%) in the placebo group and present for 2 participants (3.2%) in the pegcetacoplan group versus 6 participants (9.8%) in the placebo group. Findings related to accepted prognostic indicators for the disease (total activity score and chronicity score) are as follows:

- Mean (SD) total activity score was 7.4 (4.1) in the pegcetacoplan group and 8.2 (3.7) in the placebo group.
- Mean (SD) total chronicity score was 2.5 (2.5) in the pegcetacoplan group and 1.8 (2.0) in the placebo group.

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Concomitant treatments

Concomitant medications over 26 weeks for the safety set are summarised in Table 14. Of the 124 participants, 123 participants (99.2%) across both pegcetacoplan and placebo groups had at least 1 recorded concomitant medication since the first dose of pegcetacoplan. Over 90% of participants in each group were receiving treatment with ACEi/ARB during the RCP. In addition, 74.6% of participants in pegcetacoplan group and 68.9% participants in placebo group were receiving immunosuppressants during the RCP. The proportions of participants on systemic corticosteroids (39.7% in the pegcetacoplan group and 39.3% in the placebo group) and SGLT2 inhibitors (11.1% in the pegcetacoplan group and 9.8% in the placebo group) were similar across the treatment groups. Of note, the use of immunosuppressants was balanced between groups and there was no new initiation of treatment with immunosuppressants or systemic corticosteroids.

The most frequently reported immunosuppressant concomitant medications by PT were mycophenolate mofetil (70 participants [56.5%]) and tacrolimus (23 participants [18.5%]). The use of these 2 agents was balanced between groups.

The proportion of participants using the following groups of medications was at least approximately two-fold higher in the pegcetacoplan group: calcium-channel blockers, beta blockers, antihypertensives, and thyroid therapeutics. Conversely, the proportion of participants using mineral supplements was approximately two-fold higher in the placebo group. None of these treatments were expected to have an impact on proteinuria.

Table 14. Concomitant medications as standard of care for during the RCP

	Pegcetacoplan (N = 63) n (%)	Placebo (N = 61) n (%)	Overall (N = 124) n (%)
ACEi/ARB	57 (90.5)	56 (91.8)	113 (91.1)
Immunosuppressants	47 (74.6)	42 (68.9)	89 (71.8)
Mycophenolate mofetil	36 (57.1)	34 (55.7)	70 (56.5)
Mycophenolate sodium	2 (3.2)	4 (6.6)	6 (4.8)
Mycophenolic acid	4 (6.3)	1 (1.6)	5 (4.0)
Tacrolimus	12 (19.0)	11 (18.0)	23 (18.5)
Tacrolimus monohydrate	0	1 (1.6)	1 (0.8)

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Ciclosporin	0	1 (1.6)	1 (0.8)
Tocilizumab	1 (1.6)	0	1 (0.8)
Corticosteroids for systemic use	25 (39.7)	24 (39.3)	49 (39.5)
Prednisone	17 (27.0)	16 (26.2)	33 (26.6)
Prednisolone	8 (12.7)	5 (8.2)	13 (10.5)
Deflazacort	0	1 (1.6)	1 (0.8)
Hydrocortisone	0	1 (1.6)	1 (0.8)
Meprednisone	0	1 (1.6)	1 (0.8)
Methylprednisolone	0	1 (1.6)	1 (0.8)
Prednisolone hemisuccinate	0	1 (1.6)	1 (0.8)
SGLT2 inhibitors	7 (11.1)	6 (9.8)	13 (10.5)
Dapagliflozin	3 (4.8)	4 (6.6)	7 (5.6)
Dapagliflozin propanediol monohydrate	4 (6.3)	1 (1.6)	5 (4.0)
Empagliflozin	0	1 (1.6)	1 (0.8)

Concomitant medications for the safety set during the OLP are summarised in Table 15. All 118 (100%) participants who continued in the OLP, across both pegcetacoplan and placebo groups, had at least 1 recorded concomitant medication. The most frequently reported immunosuppressive concomitant medications by PT were mycophenolate mofetil (65 [55.1%]) and tacrolimus (21 [17.8%]).

Table 15. Concomitant medications for the OLP (OLP set)

	Pegcetacoplan-to-pegcetacoplan (N = 61) n (%)	Placebo-to-pegcetacoplan (N = 57) n (%)	Overall (N = 118) n (%)
Any concomitant medications	61 (100)	57 (100)	118 (100)
ACEi/ARB	58 (95.1)	52 (91.2)	110 (93.2)
Immunosuppressants	43 (70.5)	39 (68.4)	82 (69.5)
Mycophenolate mofetil	33 (54.1)	32 (56.1)	65 (55.1)
Tacrolimus	11 (18.0)	10 (17.5)	21 (17.8)
Mycophenolate sodium	2 (3.3)	5 (8.8)	7 (5.9)
Mycophenolic acid	3 (4.9)	1 (1.8)	4 (3.4)
Azathioprine	2 (3.3)	0	2 (1.7)
Tacrolimus monohydrate	0	1 (1.8)	1 (0.8)
Corticosteroids for systemic use	23 (37.7)	23 (40.4)	46 (39.0)
Prednisone	14 (23.0)	14 (24.6)	28 (23.7)
Prednisolone	8 (13.1)	6 (10.5)	14 (11.9)
Betamethasone; desloratadine	0	1 (1.8)	1 (0.8)
Cortisone	0	1 (1.8)	1 (0.8)

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Deflazacort	0	1 (1.8)	1 (0.8)
Hydrocortisone	0	1 (1.8)	1 (0.8)
Meprednisone	0	1 (1.8)	1 (0.8)
Triamcinolone acetonide	1 (1.6)	0	1 (0.8)
SGLT2 inhibitors	7 (11.5)	7 (12.3)	14 (11.9)
Dapagliflozin	3 (4.9)	4 (7.0)	7 (5.9)
Dapagliflozin propanediol monohydrate	3 (4.9)	1 (1.8)	4 (3.4)
Empagliflozin	0	1 (1.8)	1 (0.8)
Gemigliptin tartrate; metformin hydrochloride	0	1 (1.8)	1 (0.8)
Sitagliptin	1 (1.6)	0	1 (0.8)

2.3.3.2 VALE baseline characteristics

Demographics

Demographic and other baseline characteristics are summarised in Table 16 for the ITT set (N=53 as of the interim data cut off on 20th June 2024). The median age of the 120 participants who are expected to be eligible for the VALE study based on their participation in the VALIANT study was 19 years (range, 12-74) with 43.3% of the participants male and 56.7% female. Age categories included: ≤17 (44.2%), 18-65 (54.2%), and >65 (1.7%).

Table 16. Demographics for participants in VALE (ITT set)

	Total (N = 53)
Age at enrolment in Study APL2-C3G-314 (years), n	53
Mean (SD)	28.0 (16.8)
Median	22
Q1, Q3	17.0, 28.0
Min, Max	13, 75
≤ 17, n (%)	20 (37.7)
18 – 65	32 (60.4)
> 65	1 (1.9)
Sex, n (%)	
Male	24 (45.3)
Female	29 (54.7)
Race, n (%)	
American Indian or Alaskan Native	1 (1.9)
Asian	7 (13.2)
Black or African American	1 (1.9)

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Native Hawaiian or Other Pacific Islander	0
White	38 (71.7)
Other	4 (7.5)
Not reported	2 (3.8)
Ethnicity, n (%)	
Hispanic	11 (20.8)
Not Hispanic or Latino	38 (71.7)
Not reported*	3 (5.7)
Unknown	1 (1.9)
Baseline weight (kg) ^a , n	53
Mean (SD)	65.2 (15.1)
Median	63.2
Q1, Q3	54.8, 71.3
Min, Max	36.2, 114.0
Baseline height (cm) ^a , n	53
Mean (SD)	168.4 (9.5)
Median	166.0
Q1, Q3	162.0, 173.9
Min, Max	150.9, 190.0
Baseline BMI (kg/m ²) ^{a,b} , n	53
Mean (SD)	23.1 (5.5)
Median	21.6
Q1, Q3	19.7, 24.9
Min, Max	15.9, 41.7
Baseline systolic blood pressure (mm Hg) ^a , n	53
Mean (SD)	120.0 (13.0)
Median	121.0
Q1, Q3	111.0, 127.0
Min, Max	96, 165
Baseline diastolic blood pressure (mm Hg) ^a , n	53
Mean (SD)	73.7 (11.9)
Median	72.0
Q1, Q3	66.0, 82.0
Min, Max	37, 107

Abbreviations: BMI, body mass index; ITT, intent-to-treat; Max, maximum; Min, minimum; n, number of evaluable participants; N, number of participants; Q, quartile. ^a Baseline demographics characteristics were summarised using VALE study baseline. The VALE study baseline was defined as the last available non-missing assessment prior to first study drug administration in study APL2-C3G-314/VALE. ^b BMI (kg/m²) = Weight(kg)/(Height[m])². * Because some countries do not allow the collection of ethnicities, there were some participants with ethnicity not reported.

Disease characteristics

Baseline disease characteristics for VALE are based on the baseline from the VALIANT Study. For the available interim CSR, medical history data of VALE

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participants have not been summarised. After enrolment of this long-term safety and efficacy study is completed, those medical history data will be summarised and included in future report(s). However, this is not expected during the course of this technology appraisal.

Concomitant treatments

Nearly all the participants (52 of 53 [98.1%]) used concomitant medications during the study. The most frequently ($\geq 20\%$) used concomitant medications included: agents acting on the renin-angiotensin system (98.1%); vitamins (73.6%), immunosuppressants (66.0%); anti anaemic preparations (64.2%); lipid modifying agents (47.2%); antibacterials for systemic use, corticosteroids for systemic use, diuretics, drugs for acid related disorders, and psycholeptics (32.1% each); analgesics and beta blocking agents (26.4% each); calcium channel blockers (24.5%); mineral supplements and sex hormones and modulators of the genital system (22.6% each).

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

In appendix B, provide details of the numbers of participants eligible to enter the studies.

A summary of the statistical analysis for VALIANT and VALE is available in Table 17.

Table 17. Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT05809531 (VALIANT)	The primary efficacy endpoint is the log-transformed ratio of UPCR at week 26 compared to baseline. The null ($H_{1,0}$) and alternative ($H_{1,1}$) hypotheses for the primary efficacy analysis are: $H_{1,0}$: There is no difference in log-transformed ratio of UPCR at week 26 compared to baseline between the pegcetacoplan and placebo treatment groups. $H_{1,1}$: There is a difference in log-transformed ratio of UPCR at week 26 compared to baseline between the pegcetacoplan and placebo treatment groups.	Efficacy end points were analysed in the intent-to-treat (ITT) set. The safety set included all patients who received ≥ 1 dose of study treatment. All statistical tests were performed at 2-sided 5% level of significance and all confidence intervals were two-sided 95% confidence intervals. Continuous outcomes were analysed using a mixed-effects model for repeated measures, including fixed categorical effects and fixed covariate of the baseline value of the end point. A logistic regression model (including treatment group as an independent variable and adjusted for baseline value of the variable[s] to define the end point, disease type, and stratification factors) was used to analyse binary outcomes. An analysis of covariance was used to analyse C3G histologic index activity score with treatment as a fixed effect adjusted for baseline score of the end point, disease type, and stratification factors. The data cut-off for this primary analysis (RCP) was June 20, 2024.	Approximately 80 to 100 participants, including patients with native kidney disease or post-transplant, will be randomised 1:1 to pegcetacoplan or placebo with 40 to 50 participants per arm. Based on preliminary data from Study APL2-201, a reduction of 60% in UPCR in the pegcetacoplan group at week 26 is assumed vs a reduction of 20% in UPCR in the placebo arm, which corresponds to a mean log ratio to baseline of -0.92 vs -0.22 respectively, and a standard deviation of 0.88 (on log-scale). Based on this assumption, a sample size of 70 participants in total provides at least 90% power at 1-sided significance level of 0.025. Considering a 10% attrition to account for potential missing assessments and the impact of coronavirus disease 2019 (COVID-19), it is expected that at least 78 participants with native kidney disease should be enrolled. A minimum of 63 participants with C3G in native kidneys will	The primary analysis, including all efficacy and safety end points at 26 weeks, was conducted when all patients completed the Week 26 assessment or discontinued. An eCRF was used to permit consistent data collection; data were verified through both manual and electronic checks to ensure data integrity and accuracy. For summary of disposition, the number and percentage of participants who were treated, who were ongoing with study treatment, who completed study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, who completed the study, who withdrew from the study with a primary reason for withdrawal will be summarised and listed using the ITT set.

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		To preserve the overall type I error among the primary endpoint and key secondary endpoints, the secondary endpoints were analysed using a fixed-sequence hierarchical testing strategy. Hence, the statistical significance of the first secondary endpoint was evaluated only if statistical significance was achieved with the primary analysis of the primary endpoint. Analysis of the remaining key secondary endpoints also adhered to this hierarchical testing strategy	be enrolled, which is approximately 80% of the enrolled participants with native kidney disease.	
NCT05809531 (VALE)	N/A. This a long-term extension study from VALIANT. The study is open-label, single arm and non-randomised.	Efficacy endpoints will be performed based on the ITT set. Subgroup analysis will be performed on disease type and transplant history. The safety set includes all enrolled participants who receive at least one dose of pegcetacoplan in the study. Data from the antecedent study (VALIANT) were pooled for analyses based on pretreatment baseline (defined as realigned baseline) or VALE baseline. Descriptive statistics will be used to summarise continuous variables (e.g. n, mean, standard deviation,) and categorical data summarised using counts and percentages.	Participants who have completed the VALIANT study will be eligible to participate in this trial. The number of participants will, therefore, not exceed the maximum number of participants planned for VALIANT, which is approximately 124.	All data will be used as reported; any decisions to remove data would be made and documented prior to database lock.

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2.4.1 VALIANT study

Unless otherwise noted, the following randomisation stratification factors were adjusted for analysis of efficacy endpoints in the overall population:

- Participants with posttransplant recurrence versus nontransplant participants
- Participants with baseline renal biopsies versus participants without baseline renal biopsies

If participants were found to have had the incorrect stratum assigned at randomisation, they were analysed according to the randomisation stratum.

2.4.1.1 Analyses populations

Screened set

The screened set included all participants who provide written informed consent. This set was only used for the purpose of describing participant disposition.

Intent-to-Treat Set

The intent-to-treat (ITT) set included all participants who are randomised. Participants were to be analysed according to their assigned treatment, regardless of the treatment actually received. All efficacy analyses were performed with the ITT set.

Safety Set

The safety set included all participants who received at least 1 dose of study drug in the RCP. Participants were analysed according to the treatment they received. All safety analyses were performed with the safety set.

Per-Protocol Set

The per-protocol (PP) set included all participants in the ITT set who had not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of participants from the PP analysis set were made and documented prior to database lock. Deviations that affect exclusion from the PP set are a subset of protocol deviations; major protocol deviations did not necessarily result in exclusion of the participant from the PP set.

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2.4.2 VALE study

2.4.2.1 Analysis populations

Intent-to-Treat (ITT) Set:

The ITT set includes all enrolled participants who receive at least one dose of pegcetacoplan in the study.

Safety Set:

The safety set includes all enrolled participants who receive at least one dose of pegcetacoplan in the study.

Re-aligned Intent-to-Treat Set

The re-aligned ITT set includes all participants from the VALIANT Study who received at least one dose of pegcetacoplan in the VALIANT study.

Re-Aligned Safety Set

The re-aligned safety set includes all participants from VALIANT who received at least one dose of pegcetacoplan in the study. Analysis including data from the VALIANT study (e.g. based on the ITT Set, Re-Aligned ITT Set, or Re-Aligned Safety Set, etc.) will be noted as 'Combined Analysis'.

2.5 Critical appraisal of the relevant clinical

Effectiveness evidence

VALIANT and VALE trials were assessed for quality using the York Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare. The summary of the findings is presented in Table 18 and Table 19, and the risk of bias assessment for each study is presented in Appendix B: Identification, selection and synthesis of clinical evidence.

Table 18. Quality assessment results for parallel group RCTs

Trial number (acronym)	NCT05809531 (VALIANT)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes

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Trial number (acronym)	NCT05809531 (VALIANT)
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Table 19. Quality assessment results for non-randomised and non-controlled studies

Study name	NCT05809531 (VALE)
Was the cohort recruited in an acceptable way?	Yes
Was the exposure accurately measured to minimise bias?	Yes
Was the outcome accurately measured to minimise bias?	Yes
Have the authors identified all important confounding factors?	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes
Was the follow up of patients complete?	N/A, trial is ongoing
How precise (for example, in terms of confidence interval and p values) are the results?	Yes

2.5.1 Measures to minimize bias

2.5.1.1 VALIANT study

Participants were randomised to receive pegcetacoplan or placebo in a ratio of 1:1 via stratified permuted block randomisation with a block size of 4. The randomisation was performed centrally. To achieve balance between the arms, 2 stratification factors were applied to the randomisation. The first stratification factor examined participants with posttransplant recurrence vs nontransplant participants; at least 78 participants with C3G or IC-MPGN in the native kidneys were enrolled. This was followed by the second stratification factor, which examined participants with baseline renal biopsies (either collected during screening or a historic biopsy collected within 28 weeks prior to randomisation) vs participants without baseline renal biopsies. The stratification ensured a balance between treatment groups for the stratification factors.

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Dosing was double-blinded in the RCP; the OLP was not blinded. All central evaluations (including evaluation of renal biopsies by the central pathologist) were blinded to treatment assignment. Participants, the sponsor, investigators, and all study site personnel conducting study-related activities remained blinded to treatment allocations during the RCP at least until all participants had completed the week 26 assessments and the RCP portion of the database had been locked. Although treatment in the OLP was not blinded, investigators, study site personnel, and participants remained blinded to the RCP treatment.

2.5.1.2 VALE study

This is a single-arm non randomised study to evaluate the long-term safety and efficacy of pegcetacoplan in patients with C3G or IC-MPGN who have completed participation in the VALIANT study and who, in the opinion of the investigator, have experienced clinical benefit from pegcetacoplan administration. The study is not blinded.

2.5.2 Generalisability of the evidence to routine clinical practise in England

2.5.2.1 VALIANT and the long-term extension study VALE

Data from the VALIANT trial provide evidence positioning pegcetacoplan, a complement inhibitor targeting C3/C3b, as the first therapy to offer clinically meaningful benefits for proteinuria, eGFR stabilisation and histopathological improvements in adult and adolescent patients with C3 glomerulopathy (C3G) or primary IC-MPGN. The VALIANT Phase 3 study is the largest single trial conducted in C3G and primary IC-MPGN and is the only study to include adolescent and adult patients, with native and post-transplant kidneys. The inclusion of post-transplant participants with C3G or primary IC-MPGN recurrence was warranted given that the underlying pathophysiology of complement dysregulation is the same for native or post-transplant recurrent disease (103). Patients also received pegcetacoplan (or placebo) in addition to any pre-existing standard of care.

Patients who previously completed VALIANT were eligible to participate in VALE and who, in the opinion of the investigator, had experienced clinical benefit from Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

pegcetacoplan administration. Overall, the VALIANT and VALE studies were generally representative of a real-world C3G or primary IC-MPGN population with the exception of patients with CKD stages 4 or 5, who were excluded from the study based on their baseline eGFR being <30 ml/min per 1.73 m^2 . At CKD stages 4+ the likelihood of treatment success is more limited and are thus typically removed from clinical trials.

2.6 Clinical effectiveness results of the relevant studies

2.6.1 VALIANT study clinical effectiveness

2.6.1.1 Primary efficacy outcome

Log-transformed ratio of UPCR at week 26 compared to baseline

The primary efficacy endpoint in the VALIANT study was met, demonstrating a statistically significant reduction from baseline in log-transformed FMU UPCR at Week 26 in the pegcetacoplan group compared to the placebo group.

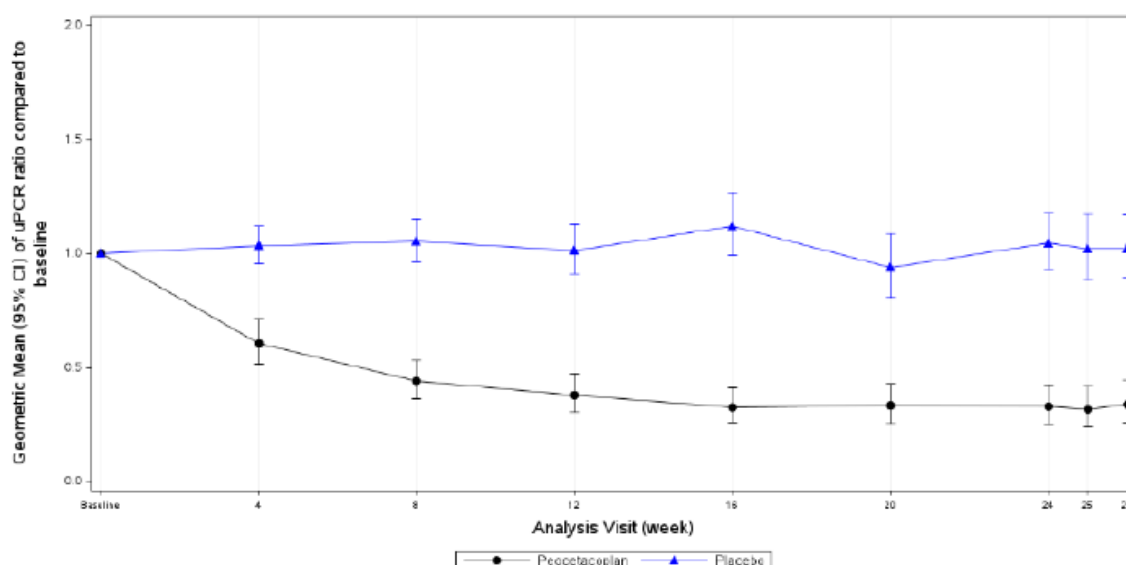
The geometric mean (95% CI) of the ratio comparing FMU UPCR at week 26 to baseline was 0.33 (0.25-0.43) for the pegcetacoplan group and 1.03 (0.91-1.16) for the placebo group, indicating a 67.2% proteinuria reduction at week 26 in the pegcetacoplan group and a 2.9% increase in proteinuria at week 26 in the placebo group compared to baseline.

The difference in LS mean of log-transformed UPCR between pegcetacoplan and placebo was -1.14 (95% CI: -1.44 to -0.85); $P < .0001$. This is equivalent to a relative reduction of 68.1% (95% CI: 57.3%-76.2%) of pegcetacoplan compared to placebo.

Figure 6 shows the geometric mean of UPCR ratio compared to baseline over the course of the 26-week RCP. These results demonstrate that the reduction in proteinuria occurred rapidly (as early as the first time point measured [4 weeks]) and was sustained through the 26-week RCP. In contrast, UPCR remained relatively unchanged in the placebo group over the same period.

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Figure 6: Geometric mean (95% CI) of UPCR Ratio Compared to Baseline for RCP (ITT Set)



Abbreviations: FMU = first-morning spot urine; ITT = intent-to-treat; LS = least-square; MMRM = mixed-effect model for repeated measures; UPCR = urine protein-to-creatinine ratio.

2.6.1.2 Key secondary efficacy outcomes

To preserve the overall type I error among the primary endpoint and key and additional secondary endpoints, a fixed-sequence testing strategy was used; hence, statistical significance of the first secondary endpoint was evaluated only if statistical significance was achieved with the primary analysis of the primary endpoint. The remaining secondary endpoints also adhered to this testing strategy and were analyzed in the order presented below (Table 20.) Overall, analyses of the key secondary endpoints demonstrate consistent and robust treatment effects of pegcetacoplan across important measures of disease activity, specifically in proteinuria reduction, decrease in C3c staining, and stabilisation of kidney function measured by eGFR in patients with C3G or IC-MPGN.

Table 20. Key secondary efficacy endpoints at Week 26 (ITT Set)

Endpoint	Pegcetacoplan	Placebo	Comparison between groups
Proportion of participants achieving the composite renal endpoint (n, %)	N = 63 31 (49.2)	N = 61 2 (3.3)	Odds ratio (95% CI) 27.48 (6.09-123.85) P < .0001

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Proportion of participants with $\geq 50\%$ reduction in UPCR (n, %)	N = 63 38 (60.3)	N = 61 3 (4.9)	Odds ratio (95% CI) 30.901 (8.39-113.77) P < .0001
Change in the activity score of the C3G histologic index score from baseline (LS mean, 95% CI)	N = 35 -3.48 (-4.72 to -2.24)	N = 34 -2.48 (-3.77 to -1.19)	Difference (95% CI) in LS mean -1.00 (-2.80, 0.79) P = .2753
Proportion of participants showing decreases in C3c staining on renal biopsy from baseline (n, %)	N = 35 26 (74.3)	N = 34 4 (11.76)	Odds ratio (95% CI) 27.39 (6.48-115.85) Nominal P < .0001
Change in eGFR from baseline (LS mean, 95% CI)	N = 63 -1.49 (-5.89, 2.89)	N = 61 -7.81 (-11.57 to -4.05)	Difference (95% CI) in LS mean 6.31 (0.50-12.12) Nominal P = .0333

Abbreviations: C3G, C3 glomerulonephritis; eGFR, estimated glomerular filtration rate; LS, least-square; UPCR, urine protein-to-creatinine ratio. ^a The composite renal endpoint was defined as achieving both a stable or improved eGFR compared to baseline (defined as $\leq 15\%$ reduction in eGFR) and a $\geq 50\%$ reduction in UPCR compared to baseline. ^b The logistic model included treatment group as independent variable and adjusted for baseline values, disease type, and stratification factors. A composite strategy was used where the response status at or after the occurrence of any of the intercurrent events was regarded as non-responder. Participants with missing outcome values other than intercurrent events were regarded as non-responder. ^c Renal biopsy endpoints were only evaluated for adult patients. Renal biopsies were not required for participants younger than 18 years of age.

Proportion of participants achieving the composite renal endpoint

A participant met the requirements of the composite renal endpoint at week 26 if they: 1. Had a stable or improved eGFR at week 26 compared to baseline ($\leq 15\%$ reduction in eGFR), and 2. Had a $\geq 50\%$ reduction in UPCR at week 26 compared to baseline.

Pegcetacoplan treatment resulted in statistically significantly more patients meeting the composite renal endpoint at Week 26 vs. placebo (49.2% in the pegcetacoplan group vs 3.3% in the placebo group). There was a 27-fold increase (OR: 27.48; 95% CI: 6.09-123.85; P < .0001) in the odds of participants meeting this composite endpoint at Week 26 with pegcetacoplan treatment vs placebo (Table 21).

Table 21. Analysis of proportion of participants who met criteria for achieving a composite renal endpoint at Week 26 with logistic model by treatment group (ITT Set)

Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)

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Participants who achieved the composite renal endpoint, n (%)	31 (49.2)	2 (3.3)
Participants with stable or improved eGFR compared to baseline ($\leq 15\%$ reduction in eGFR), n (%)	43 (68.2)	36 (59.0)
Participants with $\geq 50\%$ reduction in UPCR compared to baseline, n (%)	38 (60.3)	3 (4.9)
Estimates/comparisons at Week 26		
Proportion (SE)	0.49 (0.14)	0.03 (0.028)
95% CI of proportion	(0.25-0.74)	(0.01-0.16)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.46 (0.21-0.70)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	27.48 (6.09-123.85)	
P value (pegcetacoplan vs placebo)	<.0001	

Abbreviations: eGFR, estimated glomerular filtration rate; FMU, first-morning spot urine; ITT, intent-to-treat; UPCR, urine protein-to-creatinine ratio. Notes: Baseline eGFR value was calculated using the last non missing assessment prior to first dose. Baseline UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. Week 26 eGFR value was calculated based on the week 26 assessment result. Week 26 UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 FMU samples collected in week 24, week 25, and week 26. Participants who met criteria for achieving a composite renal endpoint were defined as: (1) a stable or improved eGFR compared to baseline ($\leq 15\%$ reduction in eGFR), and (2) a $\geq 50\%$ reduction in UPCR compared to baseline. The logistic model included treatment group as independent variable and adjusted for baseline eGFR values, baseline log-transformed UPCR values, disease type, and stratification factors. A composite strategy was used where the composite renal endpoint status at or after the occurrence of any of the ICEs were regarded as non-responder. Participants with missing eGFR and/or UPCR values at week 26 for reasons other than ICEs were regarded as non-responder.

Proportion of participants with a reduction of at least 50% from baseline in UPCR

Pegcetacoplan treatment resulted in a statistically significantly higher proportion of participants achieving a 50% reduction in UPCR at week 26 (60.3% of participants in pegcetacoplan compared to 4.9% of participants in placebo). There was a 31-fold increase (OR: 30.90; 95% CI: 8.39-113.78; $P < .0001$) in the odds of participants achieving a 50% reduction in UPCR at week 26 with pegcetacoplan treatment vs placebo (Table 22). As mentioned in section 1.3.3.1 and section 1.3.4, a reduction in uPCR of this magnitude demonstrates a clinically meaningful and important change based on established clinical thresholds, particularly when compared to what may be considered based on current best supportive care.

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Table 22. Analysis of proportion of participants who achieved a reduction of $\geq 50\%$ from baseline in FMU UPCR at Week 26 with logistic model by treatment group (ITT Set)

Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
Participants with $\geq 50\%$ reduction in UPCR compared to baseline (n [%])	38 (60.3)	3 (4.9)
Estimates/comparisons at Week 26		
Proportion (SE)	0.57 (0.13)	0.04 (0.031)
95% CI of proportion	(0.31-0.79)	(0.01-0.16)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.53 (0.29-0.76)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	30.90 (8.39-113.78)	
P value (pegcetacoplan vs placebo)	<.0001	

Abbreviations: FMU, first-morning spot urine; ITT, intent-to-treat; UPCR, urine protein-to-creatinine ratio. Notes:

Baseline UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. Week 26 UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 FMU samples collected in week 24, week 25, and week 26. The logistic model included treatment group as an independent variable and adjusted for baseline log-transformed UPCR values, disease type, and stratification factors. A composite strategy was used where the responding status at or after the occurrence of any of the ICEs was regarded as non-responder. Participants with missing UPCR values at week 26 for reasons other than ICEs were regarded as non-responder.

Change from baseline in the activity score of the C3G histologic index score

In the VALIANT Study, renal biopsy was required for enrolment (baseline) and at week 26 for adults. Therefore, renal biopsy endpoints were only evaluated for adult participants (35 participants in the pegcetacoplan group and 34 participants in the placebo group).

Despite a larger numerical decrease (improvement) in total activity score of the C3G histologic index in pegcetacoplan group, no statistically significant difference was observed between the groups at week 26 as shown in Table 23 (LS mean [95% CI] of change from baseline in the pegcetacoplan group was -3.48 [-4.72 to -2.24] compared to -2.48 [-3.78 to -1.19] in the placebo group; adjusted mean difference [95% CI] -1.00 [-2.80 to 0.79], $P = .2753$).

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Table 23. Analysis of CFB to Week 26 in C3G histologic index score with ANCOVA model by treatment group (ITT Set)

	Pegcetacoplan (N = 35)	Placebo (N = 34)
Number of participants included in the model	35	34
Estimates/Comparisons at Week 26		
LS mean (SE)	-3.48 (0.63)	-2.48 (0.66)
95% CI of LS mean	(-4.72 to -2.24)	(-3.78 to -1.19)
Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	-1.00 (-2.80, 0.79)	
Percentage Difference (pegcetacoplan vs placebo)	40.39	
P value (pegcetacoplan vs placebo)	.2753	

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; ITT = intent-to-treat; LS = least-square. Notes: Baseline was defined as the most recent non missing measurement prior to taking the first dose of investigational product. ANCOVA model included treatment as fixed effect, adjusted for baseline C3G histologic index activity score, disease type, and stratification factors. Use of prohibited medications or rescue therapies or start renal replacement therapy was handled by hypothetical strategy, discontinuation of treatment was handled by treatment-policy strategy. model included adult participants only.

It should be noted that the C3G histologic activity score was originally designed to be a predictor of C3G disease progression at diagnosis and was not meant to measure changes between two time points (4). Thus, the utility of this scoring to measure longitudinal treatment effects in C3G is now considered questionable due to recent negative findings (89, 104).

Proportion of participants who showed decreased C3c staining from baseline

This key secondary endpoint was analysed in the ITT set with participants grouped according to the treatment assigned at randomisation. No formal statistical testing was performed for this endpoint, as hierarchical testing was stopped after the third key secondary endpoint (C3G histologic index activity score). Nominal P values are shown.

A substantially larger proportion of participants had a reduction in C3c staining on kidney biopsy (defined as a decrease of at least 2 orders of magnitude in immunofluorescence intensity from baseline) at Week 26 with pegcetacoplan treatment (74.3%) compared to placebo treatment (11.8%). There was a 27-fold increase in the odds of patients meeting C3c reduction of at least 2 orders of magnitude of intensity at Week 26 vs placebo (OR: 27.39; 95% CI [6.48-115.85];

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nominal $P < .0001$) (Table 24). These results demonstrate the effect of pegcetacoplan on the critical pathological driver (C3 deposits) in C3G and IC-MPGN. Notably, 71.4% of patients treated with pegcetacoplan achieved zero intensity of C3 staining on renal biopsy, indicating the ability of pegcetacoplan to address the underlying drivers of disease.

Table 24: Analysis of Proportion of Participants Who Showed Decreases in C3c Staining From Baseline at Week 26 With Logistic Model by Treatment Group (ITT Set)

Parameter	Pegcetacoplan (N = 35)	Placebo (N = 34)
Participants with decrease in C3c staining, n (%)	26 (74.3)	4 (11.8)
Estimates/comparisons at Week 26		
Proportion (SE)	0.91 (0.07)	0.26 (0.14)
95% CI of proportion	(0.65-0.98)	(0.08-0.60)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.64 (0.41-0.87)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	27.39 (6.48-115.85)	
P value (pegcetacoplan vs placebo)	<.0001	

Abbreviations: ICE, intercurrent event; ITT, intent-to-treat. Notes: Participants who showed decreases in C3c staining were defined as a decrease of at least 2 orders of magnitude of intensity from baseline. The logistic model included treatment group as an independent variable and adjusted for baseline C3c staining, disease type, and stratification factors. A composite strategy was used where the decrease in C3c staining status at or after the occurrence of any of the ICEs was regarded as non-responder. Participants with missing C3c staining results at week 26 for reasons other than ICEs were regarded as non-responder. Since adolescents are not required to provide post screening biopsies, this endpoint was analyzed based on adult participants only.

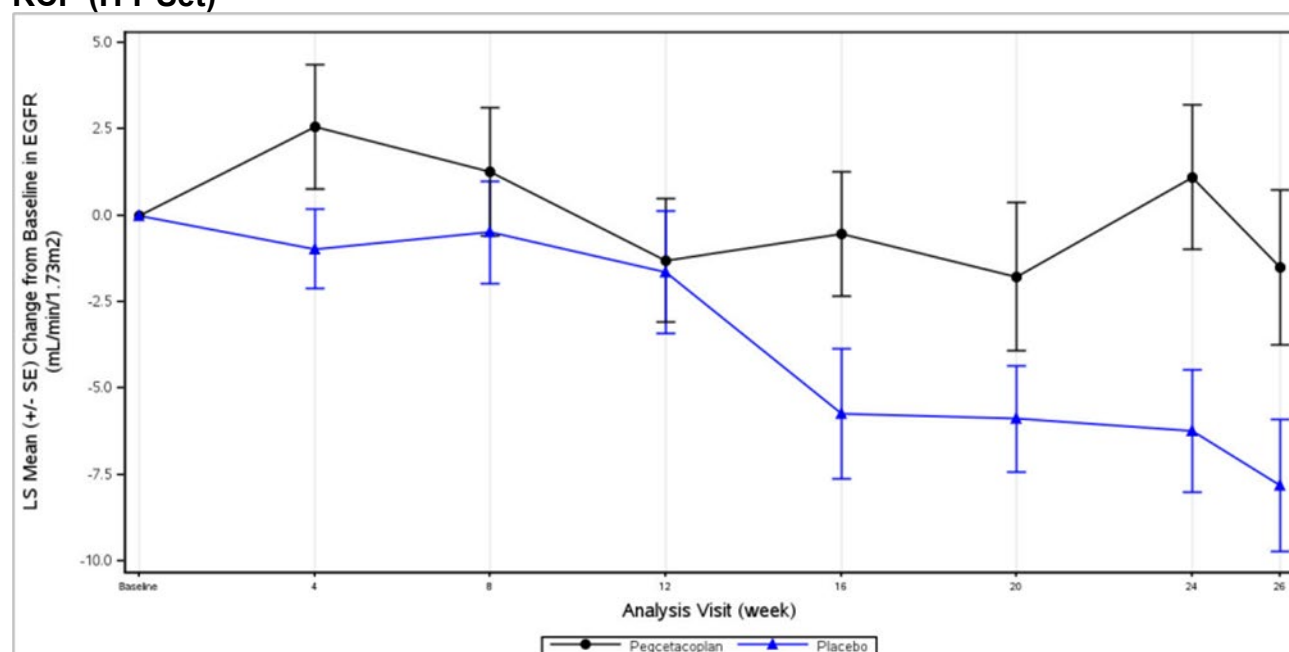
Change from baseline in eGFR

The change in eGFR from baseline to the end of the 26 week RCP was significantly less in the pegcetacoplan group (reduction of 1.5 mL/min/1.73 m²) than in the placebo group (reduction of 7.8 mL/min/1.73 m²) demonstrating that eGFR stabilized with pegcetacoplan treatment (Figure 7).

At week 26, the LS mean change (95% CI) in eGFR from baseline was -1.49 (-5.89 to 2.89) mL/min/1.73 m² in the pegcetacoplan group compared to -7.81 (-11.57 to -4.05) mL/min/1.73 m² in the placebo group. The LS mean difference (95% CI) was 6.31 (0.50-12.12) mL/min/1.73 m² with a nominal $P = .0333$, which demonstrates stabilisation of eGFR with pegcetacoplan treatment compared to placebo (Table 25).

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Figure 7: Change in eGFR over 26 Weeks of treatment from the MMRM in the RCP (ITT Set)



Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; LS = least-square; MMRM = mixed-effect model for repeated measures Notes: Baseline eGFR value was calculated using the last non missing assessment prior to the first dose. An MMRM including fixed categorical effect for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline eGFR was used to analyze the mean change from baseline to week 26 in eGFR. Use of prohibited medications or rescue therapies or start of renal replacement therapy was handled by hypothetical strategy, discontinuation of treatment was handled by policy strategy.

Overall, the LS mean changes in eGFR over time demonstrated slower eGFR decline with pegcetacoplan treatment compared to placebo and, therefore, overall stabilisation of kidney function with pegcetacoplan treatment.

No formal statistical testing was performed for this endpoint, as hierarchical testing was stopped after the third key secondary endpoint (C3G histologic index activity score). Nominal P values are displayed.

Table 25: Analysis of CFB in eGFR (mL/min/1.73 m²) With MMRM for Randomised Controlled Period (ITT Set)

Week	Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
	Number of participants included in the model	63 (100 %)	61 (100 %)
Week 26	Estimated/comparisons		

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Week	Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
	Number of participants included in the model	63 (100 %)	61 (100 %)
	LS mean (SE)	-1.49 (2.24)	-7.81 (1.92)
	95% CI of LS mean	(-5.89 to 2.89)	(-11.57 to -4.05)
	Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	6.31 (0.50-12.12)	
	Percentage difference (pegcetacoplan vs placebo)	-80.8	
	P value (pegcetacoplan vs placebo)	.0333	

Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least-square; MMRM, mixed-effect model for repeated measures. Notes: An MMRM including fixed categorical effect for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline eGFR, was used to analyze the mean change from baseline to week 26 in eGFR. Use of prohibited medications or rescue therapies or start renal replacement therapy was handled by hypothetical strategy; discontinuation of treatment was handled by treatment-policy strategy. Baseline eGFR value was to be calculated using the last non missing assessment prior to first dose.

2.6.1.3 Additional secondary efficacy endpoints

The additional secondary efficacy endpoints at week 26 were analysed in the ITT set and are summarised in Table 26. P values are all nominal and not controlled for multiplicity testing.

Table 26: Results of additional secondary efficacy endpoints at Week 26 (ITT Set)

Endpoint	Pegcetacoplan	Placebo	Comparison between groups
Proportion of participants achieving proteinuria <1 g/day (n,%)	N = 63 23 (36.5)	N = 61 7 (11.9)	Odds ratio ^a (95% CI) 5.75 (2.11, 15.72) P = .0006
Proportion of participants with baseline serum albumin levels <LLN who achieve normalisation of serum albumin levels (n, %)	N = 27 21 (77.8)	N = 23 1 (4.4)	Odds ratio ^a (95% CI) 88.34 (8.86, 880.54) P = 0001
Proportion of participants with baseline serum C3 levels <LLN who achieve serum C3 levels above LLN (n, %)	N = 41 37 (90.2)	N = 49 3 (6.1)	P = .0094

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Endpoint	Pegcetacoplan	Placebo	Comparison between groups
Change in FACIT-Fatigue Scale score from baseline (LS mean, 95% CI)	N = 63 0.93 (-1.56, 3.42)	N = 61 0.52 (-1.75, 2.79)	Difference (95% CI) in LS mean ^b 0.41 (-2.85, 3.68) P = .8054
Change in KDQOL score from baseline (LS mean, 95% CI)	N = 63 0.86 (-2.32, 4.04)	N = 61 -0.46 (-3.60, 2.69)	Difference (95% CI) in LS mean ^b 1.31 (-3.18, 5.81) P = .5664

Abbreviations: FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; KDQOL, Kidney Disease Quality of Life; LLN, lower limit of normal; LS, least-square. ^a The logistic model included treatment group as independent variable and adjusted for baseline values, disease type, and stratification factors. A composite strategy was used where the response status at or after the occurrence of any of the intercurrent events was regarded as non-responder. Participants with missing outcome values other than intercurrent events were regarded as non-responder. ^b Analysis of covariance model included treatment as fixed effect, adjusted for baseline, disease type, and stratification factors. Use of prohibited medications or rescue therapies or start of renal replacement therapy was handled by hypothetical strategy, discontinuation of treatment was handled by treatment policy strategy.

Proportion of participants achieving proteinuria <1 g/day

Pegcetacoplan treatment resulted in more participants achieving proteinuria <1 g/day (measured by 24-hour urine) at week 24 (Table 27). There was a 6-fold increase (OR pegcetacoplan vs placebo: 5.75 [95% CI: 2.11, 15.72]) in the odds of participants meeting this endpoint at week 24 with pegcetacoplan treatment vs placebo. As mentioned previously in section 1.3.3.1 and section 1.3.4, achieving a proteinuria <1 g/day is seen as a clinically relevant indicator in patients with C3G and primary IC-MPGN.

Table 27: Analysis of Proportion of Participants Achieving Proteinuria <1 g/day at Week 24 With Logistic Model by Treatment Group (ITT Set)

Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
Participants who achieved proteinuria <1 g/day, n (%)	23 (36.5)	7 (11.9)
Estimates/comparisons at week 24		
Proportion (SE)	0.27 (0.11)	0.06 (0.04)
95% CI of proportion	(0.11-0.53)	(0.02-0.19)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.21 (0.04-0.39)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	5.75 (2.11-15.71)	

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P value (pegcetacoplan vs placebo)	.0006	

Abbreviations: ICE, intercurrent event; ITT, intent-to-treat. Notes: Baseline proteinuria value was to be calculated using the last non missing assessment prior to first dose. The logistic model included treatment group as an independent variable and adjusted for baseline proteinuria values, disease type, and stratification factors. A composite strategy was used where the responding status at or after the occurrence of any of the ICEs was regarded as non-responder. Participants with missing proteinuria values at week 24 for reasons other than ICEs were regarded as non-responder.

Proportion of participants normalisation of serum albumin levels

Among participants with a baseline serum albumin concentration below the lower limit of normal (LLN), the proportion of those whose concentration was within the normal range at Week 26 was significantly greater with pegcetacoplan treatment than with placebo (21 [77.8%] vs 1 [4.3%]). The odds of meeting this endpoint were 88-fold greater with pegcetacoplan treatment than with placebo (OR: 88.34 [95% CI 8.86, 880.54]; P = 0.0001) (Table 28).

Table 28: Analysis of Proportion of Participants With Normalisation of Serum Albumin Level at Week 26 With Logistic Model by Treatment Group (ITT Set)

Parameter	Pegcetacoplan(N = 63)	Placebo(N = 61)
Participants with serum albumin levels below LLN at baseline, n	27	23
Participants with normalisation of serum albumin level, n (%)	21 (77.8)	1 (4.3)
Estimates/comparisons at week 26		
Proportion (SE)	0.79 (0.085)	0.04 (0.042)
95% CI of proportion	(0.58-0.91)	(0.01-0.26)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.75 (0.57-0.94)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	88.34 (8.86-88.54)	
P value (pegcetacoplan vs placebo)	.0001	

Abbreviations: ICE, intercurrent event; ITT, intent-to-treat; LLN, lower limit of normal. Notes: Baseline serum albumin value was calculated as the average of up to 2 serum albumin measurements preceding and including day 1. Participants were to be included in the denominator of this calculation only if the baseline albumin value is below the LLN. Week 26 serum albumin values were to be calculated as the average of up to 2 serum albumin measurements preceding and including week 26, no earlier than week 20 measurement. The logistic model included treatment group as an independent variable and adjusted for baseline albumin values, disease type, and stratification factors. A composite strategy was used where the responding status at or after the occurrence of any of the ICEs was regarded as non-responder. Participants with missing albumin values at week 26 for reasons other than ICEs were regarded as non-responder.

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Proportion of participants with baseline serum C3 levels below the LLN who achieve serum C3 levels above the LLN

Pegcetacoplan treatment was associated with more participants with baseline serum C3 levels below the LLN achieving of serum C3 levels above the LLN at week 26 than in the placebo group (37 participants [90.2%] in the pegcetacoplan group vs 3 participants [6.1%] in the placebo group) (Table 29).

Table 29: Analysis of proportion of participants with serum C3 level above LLN at Week 26 with logistic model by treatment group (ITT Set)

Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
Participants with serum C3 levels below LLN at baseline, n	41	49
Participants with serum C3 level above LLN at week 26, n (%)	37 (90.2)	3 (6.1)
Estimates/comparisons at Week 26		
Proportion (SE)	0.99 (0.023)	0.00 (0.01)
95% CI of proportion	(0.70-1.00)	(0.00-0.27)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.98 (0.93-1.04)	

Abbreviations: ICE, intercurrent event; ITT, intent-to-treat; LLN, lower limit of normal. Notes: Baseline serum C3 value was calculated as the average of up to 2 serum C3 measurements preceding and including day 1. Participants were only included in the denominator of this calculation if the baseline C3 value was below the LLN. Week 26 serum C3 value was calculated as the average of up to 2 serum C3 measurements preceding and including week 26, no earlier than week 20 measurement. The logistic model included treatment group as independent variable and adjusted for baseline C3 levels, stratification factors and disease type. A composite strategy was used where the responding status at or after the occurrence of any of the ICEs was regarded as non-responder. Participants with missing C3 levels at week 26 for reasons other than ICEs were regarded as non-responder.

Change from baseline in FACIT-fatigue scale score

No meaningful difference was observed between pegcetacoplan and placebo (LS mean [SE]) 0.93 [1.27] for the pegcetacoplan group compared to 0.52 [1.16] for the placebo group) (Table 30). This may be because most patients enrolled in VALIANT were in the earlier stages of kidney disease, with a smaller associated impact on their level of fatigue. The 26 week follow-up period may also not be long enough to see a significant impact on this outcome.

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Table 30: Analysis of change from baseline at Week 26 in FACIT-fatigue scale score with ANCOVA model by treatment group (ITT Set)

Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
Estimates/comparisons at Week 26		
LS mean (SE)	0.93 (1.27)	0.52 (1.16)
95% CI of proportion	(-1.56 to 3.42)	(-1.75 to 2.79)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.41 (-2.86 to 3.68)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	79.04	
P value (pegcetacoplan vs placebo)	.8054	

Abbreviations: ANCOVA, Analysis of covariance; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intent-to-treat; LS, least-square. Notes: Baseline was defined as the most recent non missing measurement prior to taking the first dose of investigational product. ANCOVA model included treatment as fixed effect, adjusted for baseline, disease type, and stratification factors. Use of prohibited medications or rescue therapies or start renal replacement therapy was handled by hypothetical strategy, discontinuation of treatment was handled by treatment-policy strategy.

Change from baseline in KDQOL score

No meaningful difference was observed between pegcetacoplan and placebo (LS mean [SE]) 0.86 [1.62] for the pegcetacoplan group compared to -0.46 [1.60] for the placebo group) (Table 31). As mentioned above, this may be because most patients enrolled in VALIANT were in the earlier stages of kidney disease, with a lower associated impact on their QoL. The short follow-up period may also contribute to the lack of significant differences between treatment groups.

Table 31: Analysis Changes from Baseline at Week 26 in KDQOL Score With ANCOVA Model by Treatment Group (ITT Set)

Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
Estimates/comparisons at Week 26		
LS mean (SE)	0.86 (1.62)	-0.46 (1.60)
95% CI of proportion	(-2.32 to 4.04)	(-3.60 to 2.69)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	1.31 (3.18-5.81)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	-289.14	
P value (pegcetacoplan vs placebo)	.5664	

Abbreviations: ANCOVA, analysis of covariance; ITT, intent-to-treat; KDQOL, Kidney Disease Quality of Life; LS, least-square. Notes: Baseline was defined as the most recent non missing measurement prior to taking the first dose of investigational product. ANCOVA model included treatment as fixed effect, adjusted for baseline, disease

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type, and stratification factors. Use of prohibited medications or rescue therapies or start renal replacement therapy was handled by hypothetical strategy, discontinuation of treatment was handled by treatment-policy strategy.

2.6.1.4 Key exploratory efficacy outcomes

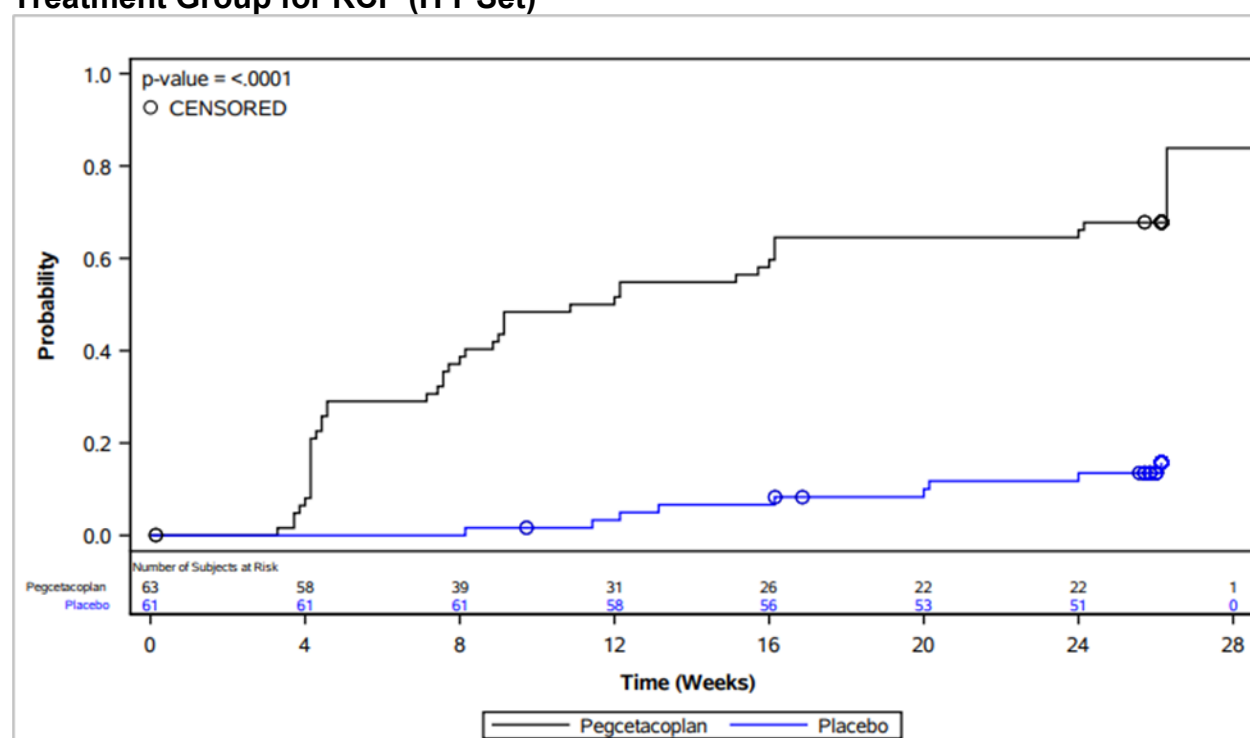
Proportion of participants with normalisation of proteinuria

Pegcetacoplan treatment was associated with a significantly greater proportion of participants (17.5%) achieving normalisation of proteinuria compared to 0% in the placebo group; $P = .0006$.

Time to 50% reduction in UPCR with a stable or improved eGFR renal composite endpoint

The number of participants meeting the definition of the composite renal endpoint 50% reduction in UPCR with a stable or improved eGFR was 44 participants (69.8%) in the pegcetacoplan group and 9 participants (14.8%) in the placebo group. The median (95% CI) time to achievement of the renal composite endpoint was 80 (54-113) days for the pegcetacoplan group (the result was NA for the placebo group) ($P < .0001$). By week 26, 67.7% of participants in the pegcetacoplan group and 13.5% of participants in the placebo group reached this endpoint. Hazard ratio (95% CI) is 8.86 (4.16-18.87) from analysis of time to 50% reduction in UPCR using a Cox proportional hazards model (Figure 8).

Figure 8: Kaplan-Meier Plot for Time to 50% Reduction in UPCR (mg/g) and Stable or Improved eGFR (mL/min/1.73 m²) Renal Composite Endpoint by Treatment Group for RCP (ITT Set)



Abbreviations: C3G, C3 glomerulonephritis; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; UPCR, urine protein-to-creatinine ratio. Notes: Participants who met criteria for event was defined as: (1) a stable or improved eGFR compared to baseline ($\leq 15\%$ reduction in eGFR), and (2) a $\geq 50\%$ reduction in UPCR compared to baseline. Cox proportional hazard model was stratified by disease type (C3G vs IC-MPGN) and stratification factors, and adjusted for baseline eGFR values and baseline log-transformed UPCR values.

Correlation analysis on reduction in UPCR and change in eGFR

Correlation analyses using Pearson and Spearman correlation tests (Table 32) were performed on the change in log-transformed FMU UPCR and change in eGFR at week 26. There was a negative correlation (for both Spearman and Pearson) between proteinuria and eGFR for the pegcetacoplan group, showing that decreasing proteinuria was correlated with increasing eGFR.

In contrast, a weak positive correlation was estimated for the placebo group between change of UPCR and eGFR. Given there was minimal change of UPCR from baseline to week 26 in placebo group, the eGFR change reflects disease progression with persistent proteinuria.

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Table 32: Correlation analysis of change in FMU UPCR (mg/g) and CFB in eGFR (mL/min/1.73 m²) at Week 26 by treatment group (ITT Set)

Pearson correlation					
			Change from baseline in eGFR		
Variable	Treatment Group	n	Correlation Coefficient (r)	P Value	95% CI
Change in log-transformed UPCR	Pegcetacoplan	56	-0.16	0.24	-0.40, 0.11
	Placebo	55	0.31	0.02	0.04, 0.53
Spearman correlation					
			Change from baseline in eGFR		
Variable	Treatment Group	n	Correlation Coefficient (r)	P Value	95% CI
Change in log-transformed UPCR	Pegcetacoplan	56	-0.29	0.02	-0.52 to -0.04
	Placebo	55	0.29	0.03	0.024 to 0.51

Abbreviations: CFB, change from baseline; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; FMU, first-morning spot urine; UPCR, urine protein-to-creatinine ratio.

Change from baseline in EQ-5D-5L score

The analysis, as specified in the SAP, was performed using the EQ-VAS measurement. Among the participants with available data (n = 71), there was no difference observed in the change from baseline in the EQ-VAS score for the pegcetacoplan group compared to the placebo group (Table 33).

Table 33: Analysis of change from baseline at Week 26 in EQ-5D-5L score with ANCOVA model by treatment group (ITT Set)

	Pegcetacoplan (N=63)	Placebo (N=61)
Number of Subjects Included in the model	33	38
Estimates/Comparisons at Week 26		
LS Mean (SE)	3.44 (2.15)	2.85 (1.99)
95% CI of LS Mean	(-0.853, 7.741)	(-1.139, 6.842)
Difference (95% CI) in LS Mean (Pegcetacoplan vs. Placebo)	0.59 (-5.42, 6.60)	
Percentage Difference (Pegcetacoplan vs. Placebo)	20.77	
p-value (Pegcetacoplan vs. Placebo)	0.8445	

Note: Baseline is defined as the most recent non-missing measurement prior to taking the first dose of investigational product. Note: Analysis of covariance (ANCOVA) model includes treatment as fixed effect, adjusted for baseline EQ-5D-5L Score, disease type, and stratification factors.

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2.6.1.5 Week 52 Overall Study (ITT Set)

All primary, key secondary, and additional secondary endpoints at week 52 were evaluated as exploratory efficacy endpoints. Unless otherwise specified, all efficacy analyses were performed on the ITT set. In the overall study, participants in the placebo-to-pegcetacoplan group had a shorter treatment duration (26 weeks) than those in the pegcetacoplan-to-pegcetacoplan group (52 weeks). Efficacy results from the placebo-to-pegcetacoplan group are generally comparable to results from the pegcetacoplan group during the RCP.

Difference in least-square means of log-transformed UPCR at week 52

The geometric mean (95% CI) of the ratio of FMU UPCRs at week 52 compared to baseline was 0.33 (0.24-0.45) for the pegcetacoplan-to-pegcetacoplan group, indicating a 67.2% proteinuria reduction, which was similar to the pegcetacoplan group during the RCP and demonstrated a sustained and durable reduction of proteinuria throughout the 52 weeks of treatment (Table 34). In the placebo-to-pegcetacoplan group, the geometric mean (95% CI) of the ratio of FMU UPCRs at week 52 compared to baseline was 0.49 (0.38-0.62), indicating a 51.3% proteinuria reduction (Table 34).

Table 34. Analysis of CFB in Log-transformed FMU UPCR (mg/g) With MMRM—Overall Study (ITT Set)

Week	Parameter	Pegcetacoplan-to-pegcetacoplan (N = 63)	Placebo-to-pegcetacoplan (N = 61)
Week 52	Estimated/comparisons ^a		
	LS mean (SE)	−1.11 (0.15)	−0.72 (0.13)
	95% CI of LS mean	(−1.42 to −0.81)	(−0.97 to −0.47)
	Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	−0.39 (−0.79 to −0.00)	
	Geometric means (95% CI) ^b	0.33(0.24-0.44)	0.487 (0.379-0.625)
	Geometric means ratios (95% CI) (pegcetacoplan vs placebo) ^b	0.67 (0.45-0.99)	

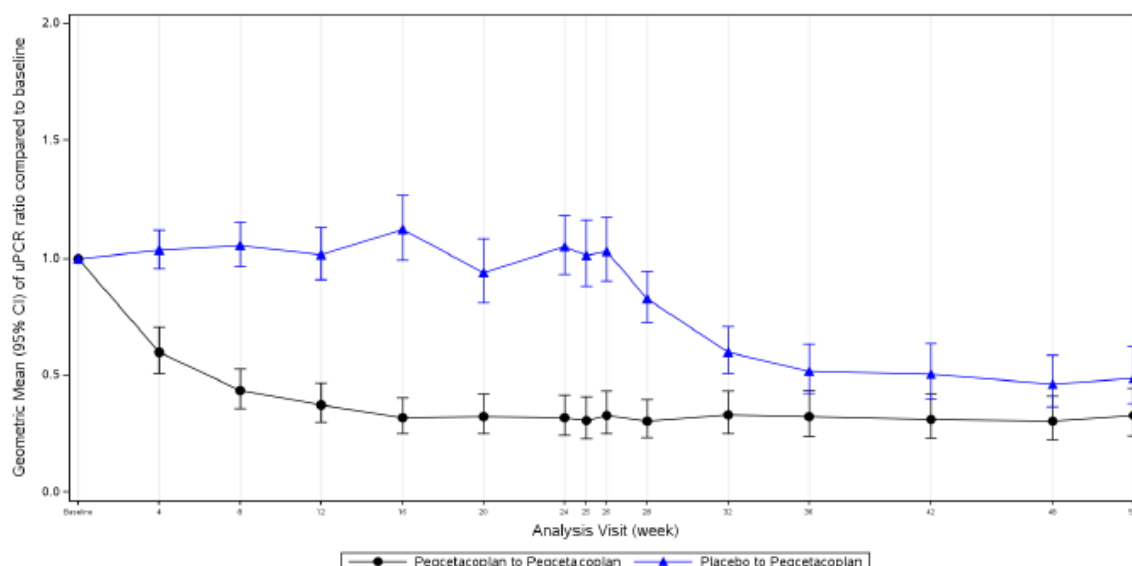
Abbreviations: CFB, change from baseline; FMU, first-morning spot urine; ITT, intent-to-treat; LS, least-square; MMRM, mixed-effects model for repeated measures; uPCR, urine protein-to-creatinine ratio. ^a An MMRM including fixed categorical effect for treatment group, visit, disease type, baseline immunosuppressants use, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline log-transformed uPCR was used to analyze the log-transformed ratio of uPCR compared to baseline.

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Missing data were imputed implicitly within the MMRM in a hypothetical strategy under the assumption of missing at random. ^b Geometric means and ratios were estimated by the exponentiated LS means and differences. Note: Baseline uPCR value was to be calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive.

Figure 9 shows the geometric mean of UPCR ratio compared to baseline throughout the overall study. These results demonstrate a sustained reduction in proteinuria in the pegcetacoplan-to-pegcetacoplan group and a rapid reduction in the placebo-to-pegcetacoplan group after beginning pegcetacoplan treatment (evident at the first time point measured [28 weeks]).

Figure 9. Geometric Mean (95% CI) Plot of CFB in Log-transformed FMU uPCR (mg/g) by Analysis Visit and Treatment Group from MMRM for Overall Study (ITT Set)



Abbreviations: CFB, change from baseline; ITT, intent-to-treat; FMU, first-morning spot urine; MMRM, mixed-effects model for repeated measures; UPCR = urine protein-to-creatinine ratio. Notes: Baseline UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. An MMRM including fixed categorical effect for treatment group, visit, disease type, baseline immunosuppressants use, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline log-transformed uPCR, was used to analyze the log-transformed ratio of uPCR compared to baseline. Missing data will be imputed implicitly within the MMRM in a hypothetical strategy under the assumption of missing at random. Geometric means are estimated by the exponentiated LS means.

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Proportion of Participants Who Met the Criteria for Achieving a Composite Renal Endpoint at Week 52

The proportion of participants who achieved the composite renal endpoint at week 52 was 38.1% in the pegcetacoplan-to-pegcetacoplan group and 36.1% in the placebo-to-pegcetacoplan group (Table 35). When compared to baseline, 61.9% of participants in the pegcetacoplan-to-pegcetacoplan group and 68.8% of participants in the placebo-to-pegcetacoplan group had a stable or improved eGFR, and 50.8% of participants in the pegcetacoplan-to-pegcetacoplan group and 40.9% of participants in the placebo-to-pegcetacoplan group had a $\geq 50\%$ reduction in UPCR. Only 3.3% of participants in the placebo group during the RCP achieved a composite renal endpoint, demonstrating a meaningful stabilisation of eGFR and reduction in proteinuria in response to starting treatment with pegcetacoplan in the OLP in this group, and a sustained response in participants in the pegcetacoplan-to-pegcetacoplan group.

Table 35. Proportion of Participants Who Met Criteria for Achieving a Composite Renal Endpoint at Week 52 by Treatment Group—Overall Study (ITT Set)

Parameter	Pegcetacoplan-to-pegcetacoplan (N = 63)	Placebo-to-pegcetacoplan (N = 61)
Participants who achieved the composite renal endpoint, n (%)	24 (38.1)	22 (36.1)
Participants with stable or improved eGFR compared to baseline ($\leq 15\%$ reduction in eGFR), n (%)	39 (61.9)	42 (68.8)
Participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%)	32 (50.8)	25 (40.9)

Abbreviations: eGFR, estimated glomerular filtration rate; ICE, intercurrent event; ITT, intent-to-treat; uPCR, urine protein-to-creatinine ratio. Notes: Baseline eGFR value was calculated using the last nonmissing assessment prior to first dose of study treatment. Baseline UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. Participants who met criteria for achieving a composite renal endpoint were defined as: (1) a stable or improved eGFR compared to baseline ($\leq 15\%$ reduction in eGFR), and (2) a $\geq 50\%$ reduction in uPCR compared to baseline. A composite strategy was used where the composite renal endpoint status at or after the occurrence of any of the ICEs was regarded as nonresponder. Participants with missing eGFR and/or UPCR values at week 52 for reasons other than ICEs were regarded as nonresponder.

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Proportion of Participants with a Reduction of at Least 50% from Baseline in UPCR at Week 52

When compared to baseline, 51% of participants in the pegcetacoplan-to-pegcetacoplan group and 41% of participants in the placebo-to-pegcetacoplan group had a $\geq 50\%$ reduction in UPCR at week 52 (Table 36). Only 4.9% of participants in the placebo group during the RCP achieved a $\geq 50\%$ reduction of UPCR, demonstrating a meaningful reduction in proteinuria in response to treatment with pegcetacoplan in the OLP.

Table 36. Proportion of Participants Who Achieved a Reduction of $\geq 50\%$ From Baseline in FMU uPCR at Week 52 by Treatment Group—Overall Study (ITT Set)

Parameter	Pegcetacoplan-to-pegcetacoplan (N = 63)	Placebo-to-pegcetacoplan (N = 61)
Participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%)	32 (50.8)	25 (40.9)

Abbreviations: FMU, first-morning spot urine; ICE, intercurrent event; ITT, intent-to-treat; UPCR, urine protein-to-creatinine ratio. Notes: Baseline UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. A composite strategy was used where the responding status at or after the occurrence of any of the ICEs was regarded as nonresponder. Participants with missing UPCR values at week 52 for reasons other than ICEs were regarded as nonresponder.

Change from baseline in eGFR at week 52

The CFB in eGFR at week 52 was analysed for the overall study ITT set and OLP set. (Table 37 and Figure 10). In the pegcetacoplan-to-pegcetacoplan group, pegcetacoplan stabilized eGFR through 52 weeks. After initially declining in the placebo-to-pegcetacoplan group, pegcetacoplan similarly stabilized eGFR for the remainder of the treatment period. After 52 weeks, the LS mean CFB in eGFR was comparable for both groups, although slightly more negative in the placebo-to-pegcetacoplan group. However, the magnitude is small and the CIs for the treatment groups overlapped (pegcetacoplan-to-pegcetacoplan) indicating that the difference between the treatment groups was not meaningful.

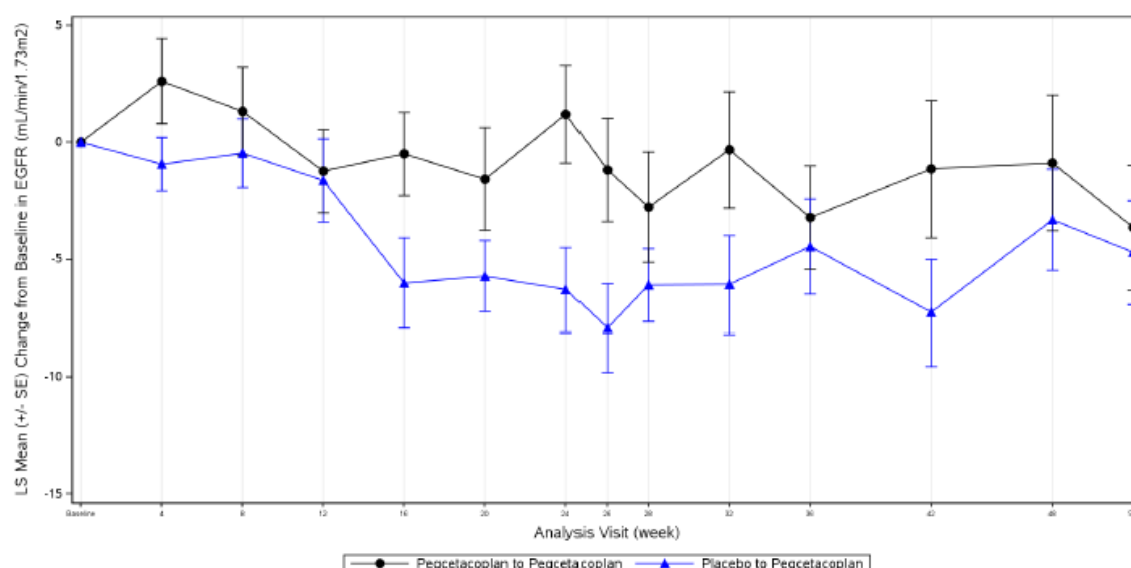
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Table 37. Analysis of CFB in eGFR (mL/min/1.73 m²) With MMRM at Week 52 for Overall Study (ITT Set)

Parameter	Pegcetacoplan-to-pegcetacoplan (N = 63)	Placebo-to-pegcetacoplan (N = 61)
LS mean (SE)	-3.65 (2.66)	-4.72 (2.23)
95% CI of LS mean	(-8.93 to 1.62)	(-9.13 to -0.31)
Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	1.067 (-5.80 to 7.94)	
Percentage difference (pegcetacoplan vs placebo)	-22.6	

Abbreviations: CFB, change from baseline; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least-square; MMRM, mixed-effects model for repeated measures. Notes: An MMRM including fixed categorical effect for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline eGFR, was used to analyze the mean CFB in eGFR. Missing data were imputed implicitly within the MMRM in a hypothetical strategy under the assumption of missing at random. Baseline eGFR value was calculated using the last nonmissing assessment prior to first dose of study treatment.

Figure 10. LS Mean ($\pm$ SE) Plot of CFB in eGFR (mL/min/1.73 m²) by Analysis Visit and Treatment Group from MMRM for Overall Study (ITT Set)



Abbreviations: CFB, change from baseline; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least-square; MMRM, mixed-effects model for repeated measures. Notes: An MMRM including fixed categorical effect for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline eGFR, was used to analyze the mean CFB in eGFR. Missing data were imputed implicitly within the MMRM in a hypothetical strategy under the assumption of missing at random. Baseline eGFR value was calculated using the last nonmissing assessment prior to first dose of study treatment.

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2.6.2 VALE study clinical effectiveness

The analyses of the long-term efficacy of pegcetacoplan to reduce UPCR and to stabilize eGFR are provided after participants received their first dose of pegcetacoplan in the VALIANT study (re-aligned baseline) through dosing in VALE. Additional analyses are provided using the VALE study baseline (prior to the first dose of pegcetacoplan in the VALE study) and using the baseline from the VALIANT study (prior to the first dose of treatment, either pegcetacoplan or placebo).

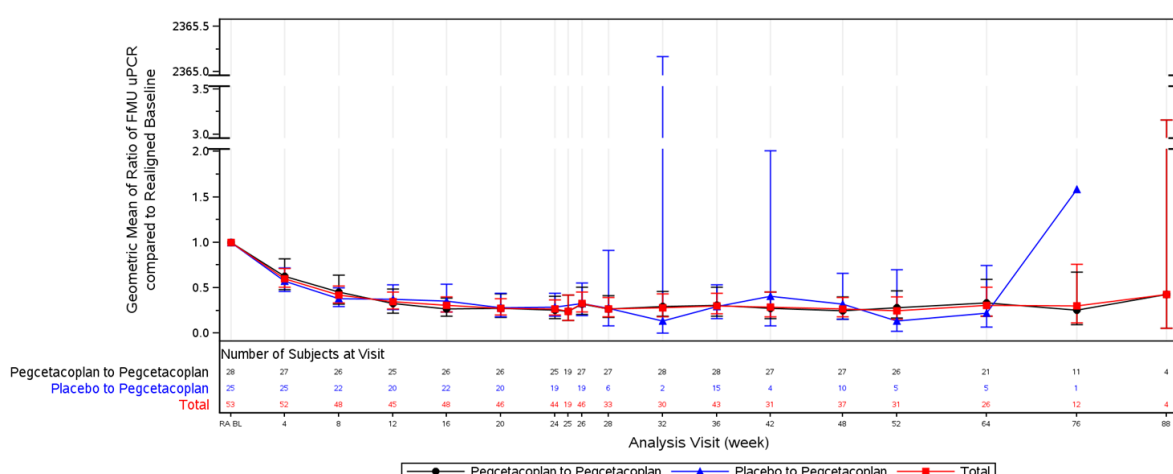
2.6.2.1 Primary efficacy outcome

Log-transformed ratio of UPCR over time

The primary efficacy endpoint in this study was presented as 1) comparison to re-aligned baseline using VALE ITT set (n=53) and re-aligned ITT set (n=120); 2) comparison to VALE study baseline using VALE ITT set (n=53); and 3) comparison to VALIANT baseline using VALE ITT set (n=124).

Figure 11 shows the geometric mean (95% CI) of the ratio of FMU UPCR at each visit compared to the re-aligned baseline (prior to the first dose of pegcetacoplan in VALIANT) for the VALE ITT set. Reductions in UPCR started as early as week 4 and persisted through week 64 after initiation of pegcetacoplan treatment.

Figure 11: Geometric Mean (95% CI) of Ratio of FMU UPCR by Visit Compared to Re-Aligned Baseline (VALE ITT Set)



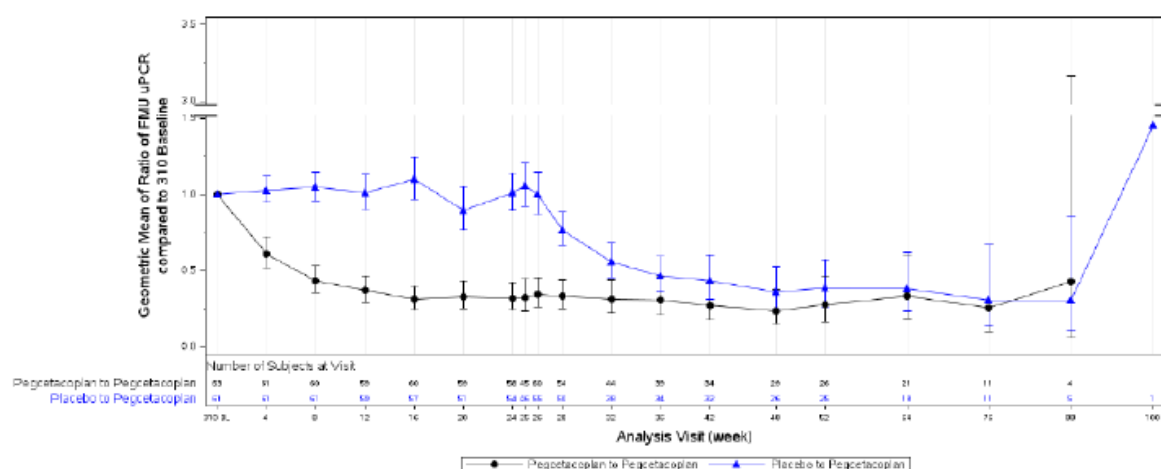
Abbreviations: FMU, first morning urine, ITT, intent-to-treat: UPCR, urine protein-to-creatinine ratio. Note: Re-aligned baseline: For participants who received pegcetacoplan during the randomised controlled period (RCP) in Study VALIANT, the baseline was defined as the baseline value used in Study VALIANT, i.e., baseline UPCR Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

values were calculated as the average of the UPCR measurements from at least 6 of the 9 first-morning spot urine (FMU) samples collected between the start of screening and day 1, inclusive. For participants who received placebo during the RCP in the antecedent study, the baseline was defined as the last available non-missing assessment prior to enrolling into the open-label period (OLP) in Study VALIANT, i.e., baseline was calculated as the average of the UPCR values from the FMU samples collected during week 24, week 25, and week 26 (or, the 3 most recent visits prior to the first administration of pegcetacoplan) in that study. Analysis visit week was counted after receiving the first dose of pegcetacoplan in Study VALIANT.

The geometric mean (95% CI) FMU UPCR at the re-aligned baseline was 2432.2 mg/g (1986.8, 2977.5). At week 64 after initiation of pegcetacoplan treatment, the geometric mean (95% CI) FMU UPCR was 758.2 mg/g (488.9, 1175.8) with the geometric mean ratio (95% CI) of week 64 to the re-aligned baseline of 0.29 (0.18, 0.47), indicating a 71% reduction from baseline.

Figure 12 displays the geometric mean ratio of FMU UPCR at each visit compared to the VALIANT baseline (prior to the first dose of treatment, either pegcetacoplan or placebo) for participants randomised in the VALIANT ITT set. Both treatment groups experienced similar reductions in UPCR after receiving pegcetacoplan, starting as early as 4 weeks after starting pegcetacoplan (week 4 for the pegcetacoplan-to-pegcetacoplan group, week 28 for the placebo-to-pegcetacoplan group) and persisting through week 76 (pegcetacoplan-to-pegcetacoplan, placebo-to-pegcetacoplan group). Geometric mean ratios decreased in both treatment groups following administration of pegcetacoplan to <0.5 (indicating >50% reduction) and were sustained.

Figure 12: Geometric Mean ($\pm$ SE) of Ratio Plot of FMU UPCR Compared to(mg/g) Results and Geometric Mean (95% CI) Using VALIANT study Baseline by Analysis Visits and Treatment Groups (VALIANT ITT Set)



Abbreviations: FMU, first morning urine; 310 BL = VALIANT baseline; ITT, intent-to-treat; UPCR, urine protein-to-creatinine ratio. Note: VALIANT baseline: The baseline was defined as the baseline value used in the antecedent study (VALIANT study) participant had enrolled in. Baseline UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 first-morning spot urine (FMU) samples collected between the start of screening and day 1, inclusive. Note: Analysis visit week was counted after receiving the first dose of pegcetacoplan in VALIANT.

Table 38 shows that at the end of the RCP (VALIANT study), there was a large difference between the treatment groups for the change from baseline in log-transformed UPCR at week 26. For the first 26 weeks, there was only the pegcetacoplan group compared to the placebo group. The pegcetacoplan group experienced a 67% reduction in UPCR compared to the placebo group with 1.9% increased UPCR. After the RCP, the placebo group transitioned to pegcetacoplan (placebo-to-pegcetacoplan group), and both treatment groups experienced reductions in UPCR, which became statistically insignificant starting at week 36, and the reduction persisted in both groups through week 76.

Table 38: Analysis of Change from VALIANT Baseline in Geometric Mean Ratio of FMU UPCR (mg/g) with MMRM for Select Visits - Combined Analysis (VALIANT ITT Set)

Analysis visit	Parameter	Pegcetacoplan to pegcetacoplan (N=63)	Placebo to pegcetacoplan (N=61)
Week 26	Estimates/comparisons ^a		

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	LS mean (SE) 95% CI of LS mean Difference (95% CI) in LS mean (pegcetacoplan vs. pegcetacoplan) <i>P</i> value (pegcetacoplan – placebo) Geometric means (95% CI) ^b Geometric means ratio (95% CI) (pegcetacoplan vs. placebo) ^b	-1.11 (0.13) -1.37 to -0.84 -1.13 (-1.42 to -0.83) < .0001 0.33 (0.25-0.43) 0.32 (0.24-0.44)	0.02 (0.07) -0.11 to 0.15 1.02 (0.89-1.16)
Week 36	Estimates/comparisons^a LS mean (SE) 95% CI of LS mean Difference (95% CI) in LS mean (pegcetacoplan vs. pegcetacoplan) <i>P</i> value (pegcetacoplan – placebo) Geometric means (95% CI) ^b Geometric means ratio (95% CI) (pegcetacoplan vs. placebo) ^b	-1.07 (0.16) -1.38 to -0.76 -0.33 (-0.71 to 0.05) 0.0839 0.34 (0.25-0.46) 0.72 (0.49-1.05)	-0.74 (0.11) -0.95 to -0.5 0.48 (0.38-0.59)
Week 52	Estimates/comparisons^a LS mean (SE) 95% CI of LS mean Difference (95% CI) in LS mean (pegcetacoplan vs. pegcetacoplan) <i>P</i> value (pegcetacoplan – placebo) Geometric means (95% CI) ^b Geometric means ratio (95% CI) (pegcetacoplan vs. placebo) ^b	-1.18 (0.17) -1.51 to -0.84 -0.29 (-0.77 to 0.17) 0.2135 0.31 (0.22-0.43) 0.74 (0.47-1.19)	-0.88 (0.17) -1.21 to -0.55 0.42 (0.29-0.58)
Week 76	Estimates/comparisons^a LS mean (SE) 95% CI of LS mean Difference (95% CI) in LS mean (pegcetacoplan vs. pegcetacoplan) <i>P</i> value (pegcetacoplan – placebo) Geometric means (95% CI) ^b Geometric means ratio (95% CI) (pegcetacoplan vs. placebo) ^b	-1.16 (0.24) (-1.63, -0.68) -0.09 (-0.72, 0.52) 0.7544 0.32 (0.19, 0.51) 0.91 (0.49, 1.69)	-1.06 (0.20) (-1.46, -0.66) 0.35 (0.23, 0.52)

Abbreviations: FMU, first-morning spot urine; ITT, intent-to-treat; LS, least square; MMRM, mixed-effects model for repeated measures; n, number of evaluable participants; N, number of participants; UPCR, urine protein-to-creatinine ratio. ^a MMRM including the fixed categorical effect for treatment group, visit, disease type, baseline immunosuppressants use, stratification factors, and the visit-by-treatment group interactions as well as the continuous fixed covariate of baseline log-transformed ratio of UPCR, was utilized to analyze the geometric mean ratio of UPCR at each visit compared to the VALIANT baseline. ^b Geometric means and ratios were estimated by exponentiated LS means and differences. Note: VALIANT study baseline: The baseline was defined as the baseline value used in the antecedent study (VALIANT) participant had enrolled in. Baseline UPCR value were calculated as the average of the UPCR measurements from at least 6 of the 9 first-morning spot urine (FMU) samples collected between the start of screening and day 1, inclusive.

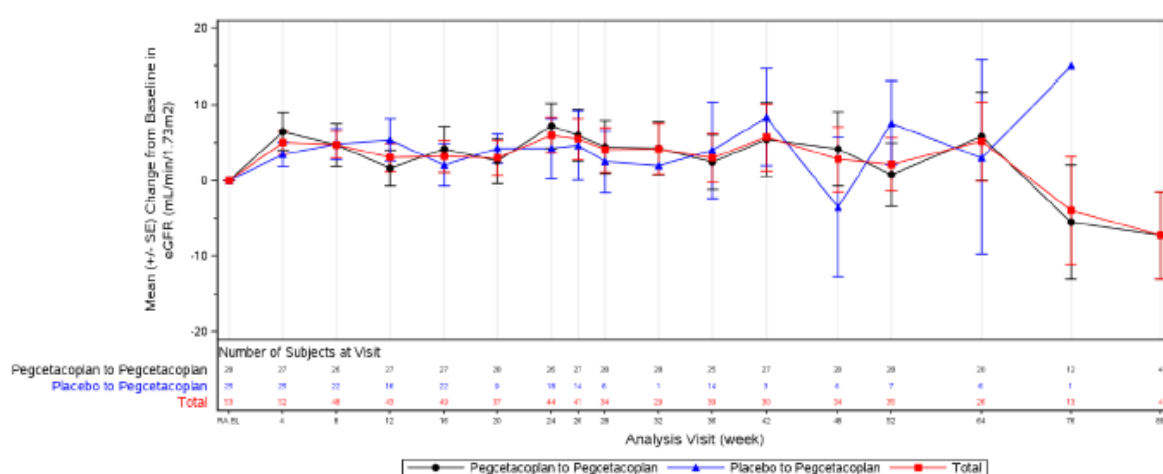
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2.6.2.2 Secondary efficacy outcomes

eGFR change over time

Figure 13 shows the mean change for participants who continued into the VALE Study (VALE ITT set). For the total group, pegcetacoplan treatment was associated with stabilisation of the eGFR. The mean ($\pm$ SE) change for eGFR in mL/min/1.73 m² slightly increased through to week 26 (5.9 [17.43]), and then remained relatively unchanged through to week 64.

Figure 13: Mean ($\pm$ SE) Change from Re-Aligned Baseline of eGFR (mL/min/1.73 m²) by Analysis Visit and Treatment Group - VALE ITT Set

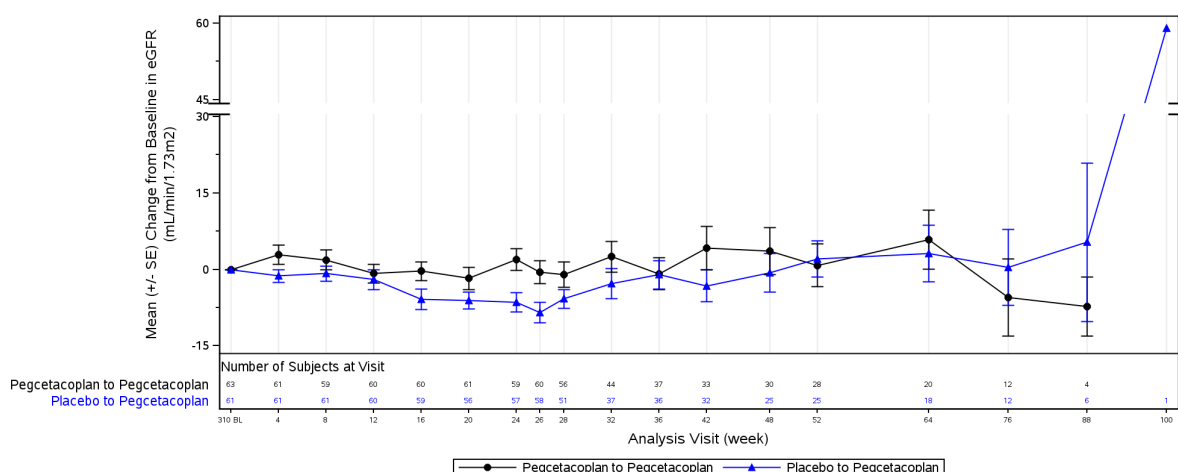


Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; RA BL, Re-Aligned Baseline. Note: Re-aligned baseline: For participants who received pegcetacoplan during the randomised controlled period (RCP) in VALIANT, the baseline eGFR value was defined as the baseline value used in VALIANT. For participants who received placebo during the RCP in the antecedent study, the baseline was defined as the last available non-missing assessment prior to enrolling into the open-label period (OLP) in VALIANT. Analysis visit week is counted after receiving the first dose of pegcetacoplan in VALIANT.

Figure 14 displays the mean ($\pm$ SE) change in eGFR from baseline over time for participants randomised in VALIANT (ITT set). For the pegcetacoplan-to-pegcetacoplan group, mean eGFR was stable through to week 64; for the placebo-to-pegcetacoplan group, mean eGFR initially decreased through to week 26 while on placebo treatment, then stabilized or slightly increased after start of pegcetacoplan treatment.

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Figure 14: Mean ($\pm$ SE) Change from VALIANT Baseline of eGFR (mL/min/1.73 m²) by Analysis Visit and Treatment Group ITT Set



Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat. Note: VALIANT study baseline: The eGFR baseline was defined as the baseline value used in the antecedent study (VALIANT) in which the participant had enrolled. Analysis visit week was counted after receiving the first dose of pegcetacoplan in the VALIANT Study.

Proportion of Participants Achieving at Least 50% Reduction in UPCR from the Pretreatment Value Over Time

Table 39 presents an analysis of the proportion of participants in the total group achieving a reduction of at least 50% from re-aligned baseline in FMU UPCR (mg/g) for VALE ITT set up to Week 64.

After 4 weeks of pegcetacoplan, 40.4% of participants achieved more than 50% proteinuria reduction. This proportion increased to 64.4% after 12 weeks of treatment with pegcetacoplan and was sustained to week 64.

Table 39: Analysis of the Total Participants Achieving a Reduction of at least 50% from Re-Aligned Baseline in FMU UPCR (mg/g) - Combined Analysis VALE ITT Set

Analysis visit ^a		Total (N=53)
Week 4	Number of evaluable participants, n	52
	Proportion of participants with $\geq 50\%$ reduction in UPCR compared to baseline, n (%)	21 (40.4)
	95% CI of proportion	27.01-54.90
Week 12	Number of evaluable participants, n	45

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	Proportion of participants with $\geq 50\%$ reduction in UPCR compared to baseline, n (%) 95% CI of proportion	29 (64.4) 48.78-78.13
Week 20	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in UPCR compared to baseline, n (%) 95% CI of proportion	46 31 (67.4) 51.98-80.47
Week 26	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in UPCR compared to baseline, n (%) 95% CI of proportion	45 32 (71.1) 55.69-83.63
Week 36	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in UPCR compared to baseline, n (%) 95% CI of proportion	42 28 (66.7) 50.45- 80.43
Week 48	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in UPCR compared to baseline, n (%) 95% CI of proportion	37 25 (66.7) 50.21-81.99
Week 64	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in UPCR compared to baseline, n (%) 95% CI of proportion	26 15 (57.7) 36.92-76.65

Abbreviations: FMU, first morning urine; ITT, intent-to-treat; n, number of evaluable participants; N, number of participants; UPCR, urine protein-to-creatinine ratio. ^a Analysis visits were based on re-aligned baseline. The visit week were counted after receiving the first dose of pegcetacoplan in VALIANT. Notes: The 2-sided 95% CI for proportion of responders was calculated using the Clopper-Pearson method. Re-Aligned baseline: For participants who received pegcetacoplan during the randomised controlled period (RCP) in VALIANT, the baseline was defined as the baseline value used in VALIANT, i.e., the average of the UPCR values from the FMU samples collected during screening and on day 1 before dosing in that study. For participants who received placebo during the RCP in the antecedent study, the baseline was defined as the last available non-missing assessment prior to enrolling into the open-label period (OLP) in VALIANT, i.e., baseline was calculated as the average of the UPCR values from the FMU samples collected during week 24, week 25, and week 26 (or, the 3 most recent visits prior to the first administration of pegcetacoplan) in that study.

Proportion of Participants with Stable or Improved eGFR Values over time

Table 40 summarises the analysis of the proportion of participants in the total group with eGFR values that are stable or improved from the re-aligned baseline for the VALE ITT set for visits up to week 64. The eGFR value was considered to be stable or improved if there was no more than a 15% reduction from the pretreatment value. The proportion of participants with stable or improved eGFR values was sustained through to week 64.

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Table 40: Analysis of the Total Participants with eGFR (mL/min/1.73 m²) Values that are Stable or Improved from Re-Aligned Baseline - Combined Analysis - VALE ITT Set

Analysis visit ^a		Total (N=53)
Week 4	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	52 50 (96.2) 86.79-99.53
Week 12	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	43 38 (88.4) 74.92-96.11
Week 20	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	37 32 (86.5) 71.23-95.46
Week 26	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	40 34 (85.0) 70.16-94.29
Week 36	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	39 30 (76.9) 60.67-88.87
Week 48	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	34 23 (67.6) 49.47-82.61
Week 64	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	26 21 (80.8) 60.65-93.45

Abbreviations: eGFR, estimated glomerular filtration rate; FMU, first morning urine; ITT, intent-to-treat; n, number of evaluable participants; N, number of participants. ^a Analysis Visits are based on re-aligned baseline. The visit week is counted after receiving the first dose of pegcetacoplan in VALIANT study. Notes: The 2-sided 95% CI for proportion of responders is calculated using the Clopper-Pearson method. Re-aligned baseline: For participants who received pegcetacoplan during the randomised controlled period (RCP) in VALIANT, the baseline was defined as the baseline value used in VALIANT. For participants who received placebo during the RCP in the antecedent study, the baseline was defined as the last available non-missing assessment prior to enrolling into the open-label period (OLP) in VALIANT.

Proportion of Participants with Proteinuria <1g/day Over Time

Table 41 summarizes the proportion of participants with <1 g/day of proteinuria by visit after starting pegcetacoplan for the 314 ITT set using the re-aligned baseline. After 12 weeks of pegcetacoplan, 44.9% of participants achieved proteinuria <1 g/day, and this was sustained at week 48 by 53.8% of participants; there are no 24-hour urine data for week 64.

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Table 41: Analysis of the Total Participants with Proteinuria < 1g/day Based on Re-Aligned Baseline – Combined Analysis (VALE ITT Set)

Analysis visit ^a		Total (N=53)
Week 12	Number of evaluable participants, n Participants achieving proteinuria < 1g/day, n (%) 95% CI of proportion	49 22 (44.9) 30.67-59.77
Week 24	Number of evaluable participants, n Participants achieving proteinuria < 1g/day, n (%) 95% CI of proportion	51 25 (49.0) 34.75-63.40
Week 36	Number of evaluable participants, n Participants achieving proteinuria < 1g/day, n (%) 95% CI of proportion	26 10 (38.5) 20.23-59.43
Week 48	Number of evaluable participants, n Participants achieving proteinuria < 1g/day, n (%) 95% CI of proportion	26 14 (53.8) 33.37-73.41

Abbreviations: ITT, intent-to-treat; n, number of evaluable participants; N, number of participants. ^a Analysis visits were based on re-aligned baseline. The visit week was counted after receiving the first dose of pegcetacoplan in VALIANT. Note: The 2-sided 95% CI for proportion of responders was calculated using the Clopper-Pearson method.

The Change from Pretreatment in the FACIT-Fatigue Scale Score

At week 52, there was not a significant change in the FACIT-Fatigue Scale Score for the total group. However, the number of participants was too small to make any meaningful summaries.

Time to Progression to a Composite Clinical Outcome (at Least One of the Following: Sustained Doubling of Serum Creatinine, Progression to Chronic Kidney Disease Stage 5 or ESRD, Renal Transplantation, or Death From Renal or Cardiovascular Disease)

The number of participants with events was too low to estimate median time to event. There was a total of 6 (5.0%) participants who met composite clinical outcome with pegcetacoplan up to 21 months.

HRQoL Assessments

The number of participants with HRQoL assessments was too small to make any meaningful summaries

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2.7 Subsequent treatments used in the relevant studies

2.7.1 VALIANT

Two participants, both in the placebo group, were administered rescue therapy over 26 weeks of the RCP.

Table 42 Subsequent treatments used in VALIANT

	Pegcetacoplan (N= 63): N (%) treated	Mean time on treatment (95% CI) (N=0) in pegcetacoplan Arm	Placebo (N= 61): N (%) treated	Mean time on treatment (95% CI) (N=2) in Arm Placebo
Methylprednisolone (1000 IV)	0 (0)	NA	1 (1.6)	3 days
Prednisolone (100-250 IV)	0 (0)	NA	1 (1.6)	14 days

2.8 Subgroup analysis

2.8.1 VALIANT study

Analyses of the primary efficacy endpoint and key secondary outcomes at week 26, by subgroup were pre-specified and were performed to evaluate the consistency of the primary analysis results across subgroups defined by demographic and baseline characteristics and included: age group, sex, race, geographic region, disease type, transplant history, baseline FMU UFCR: <3000 mg/g, ≥3000 mg/g, baseline eGFR: <60 mL/min/1.73 m², ≥60 mL/min/1.73 m², baseline C3 level: normal, below the LLN, baseline immunosuppressants use. Subgroups relevant to the decision problem included disease type (e.g. C3G or IC-MPGN) and transplant history. *P* values were not controlled for multiplicity.

For the primary efficacy endpoint, proteinuria reduction was consistent across all subgroups based on disease type (C3G vs IC-MPGN), age (adult vs adolescent), and transplant history (post-transplant vs non-transplant), (Appendix C, Figure 30).

Overall, the analysis of key secondary outcomes demonstrated consistency with the overall ITT set. The results are summarised in Appendix C.

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A subgroup analysis was also carried out for patients in VALIANT who were on concomitant immunosuppressive therapy (Sobi data on file (85)). Pegcetacoplan demonstrated favourable efficacy in both immunosuppressant (IS) -treated and non IS-treated patients. There was a 70.3% and 64.5% clinically meaningful proteinuria reduction vs placebo in IS-treated and non IS-treated patients, respectively Appendix C, Figure 32). Both groups achieved eGFR stabilisation (+6.8 and +5.0 mL/min/1.73 m² vs placebo in IS-treated and non IS-treated patients, respectively) (Appendix C, Figure 33) and 65.4% and 88.9% of IS-treated and non IS-treated patients achieved zero C3 staining in renal biopsies (Appendix C, Table 116).

A full summary of results for subgroups is included in Appendix C: Subgroup analysis.

2.9 Meta-analysis

An indirect treatment comparison was carried out in the absence of head-to-head trials.

2.10 Indirect and mixed treatment comparisons

Full details of the methodology of the indirect treatment comparison (ITC) are included in Appendix B: Identification, selection and synthesis of clinical evidence.

2.10.1 Summary of trials included in the ITC

Seven studies met the eligibility criteria and were included in the SLR. A summary of the trials is shown in Table 43.

Table 43. Summary of trials included in the SLR

Study Name	Intervention/comparator	Disease	Publications
NOBLE (NCT04572854)	Pegcetacoplan vs SOC	Recurrent C3G and IC-MPGN	(89)
DISCOVERY (NCT03453619)	Pegcetacoplan	Native C3G	(79)
VALIANT (NCT05067127)	Pegcetacoplan vs placebo	Native and recurrent C3G and IC-MPGN	(85, 94-100)
NCT038321146	Iptacopan	Native and recurrent C3G	(105)
NCT03955445	Iptacopan	Native and recurrent C3G	(106)

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(extension of NCT03832114)			
APPEAR-C3G (NCT04817618)	Iptacopan vs placebo + SOC	Native C3G	(107-110)
Pooled iptacopan analysis	Iptacopan	Native C3G	(111)

^aRecurrent disease is defined as C3G/IC-MPGN after kidney transplant and native disease is defined as C3G/IC-MPGN that is not recurrent

Two studies were assessed for similarity in terms of outcome definitions and timepoints (112, 113). Both studies could facilitate an indirect comparison between pegcetacoplan and iptacopan with placebo as the common comparator. A full description of the methodology of the indirect treatment comparison is provided in Appendix B. The selected trials and the interventions are summarised in Table 44.

Table 44. Summary of trials used to carry out the indirect treatment comparison

Study Name	Pegcetacoplan	Placebo	Iptacopan
VALIANT (NCT05067127)	Yes	Yes	No
APPEAR-C3G (NCT04817618)	No	Yes	Yes

2.10.2 Results

Outcome definitions for each of the studies were compared and 6 were found to be consistent across both trials:

- Log-transformed ratio of UPCR compared to baseline
- Proportion of participants achieving composite renal endpoint
- Proportion of participants with at least 50% reduction in UPCR
- Change from baseline in activity score of the histologic index
- Change from baseline in eGFR
- Change from baseline in patient-reported fatigue (FACIT score).

However, minor discrepancies in the definitions of these outcomes were noted between the VALIANT and APPEAR-C3G trials. Despite these differences, the

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definitions were deemed sufficiently consistent to conduct a Bucher's indirect treatment comparison between pegcetacoplan and iptacoplan.

2.10.2.1 Proteinuria

In both studies, the primary outcome was the percent change from baseline in log transformed UPCR, measured as FMU in VALIANT and 24-hour urine in the APPEAR C3G trial. In both trials, the primary outcome was assessed with the MMRM model using data with multiple imputations.

Bucher's indirect comparison of the primary outcomes from VALIANT and APPEAR C3G found that after 6 months of treatment, pegcetacoplan resulted in a significantly greater reduction in UPCR from baseline compared with iptacoplan (%MD = -50.90 [-67.34; -26.18]) (Table 45, Figure 15). Analyses using the same UPCR measurement method included only non-missing values of UPCR (24h) from VALIANT (%MD = -47.28 [-65.83; -18.67]) and non-missing only values of UPCR (FMU) from APPEAR C3G (%MD = -51.66 [-70.38; -21.11]). The results of these analyses were consistent with results from the primary outcomes and also found that pegcetacoplan resulted in a statistically significant greater reduction in UPCR from baseline than iptacoplan (Table 45, Figure 15).

Pegcetacoplan was also associated with a significantly higher probability of achieving a UPCR <1 g/g (RD = 0.26 [0.06; 0.46]) and achieving ≥50% reduction of UPCR (RD = 0.29 [0.01; 0.58]) than iptacoplan. As mentioned in section 1.3.4, both are clinically relevant indicators of improvements for patients with C3G and primary IC-MPGN, and are aligned with the definition of response used in the cost-effectiveness model. Comparisons based on odds ratios did not reach statistical significance (UPCR <1 g/g OR = 2.11 [0.30; 14.61]; UPCR ≥50% reduction OR = 4.46 [0.57; 34.84]) (Table 45, Figure 15).

Table 45. Results of Bucher's indirect comparison between Pegcetacoplan and Iptacoplan for proteinuria-related outcomes.

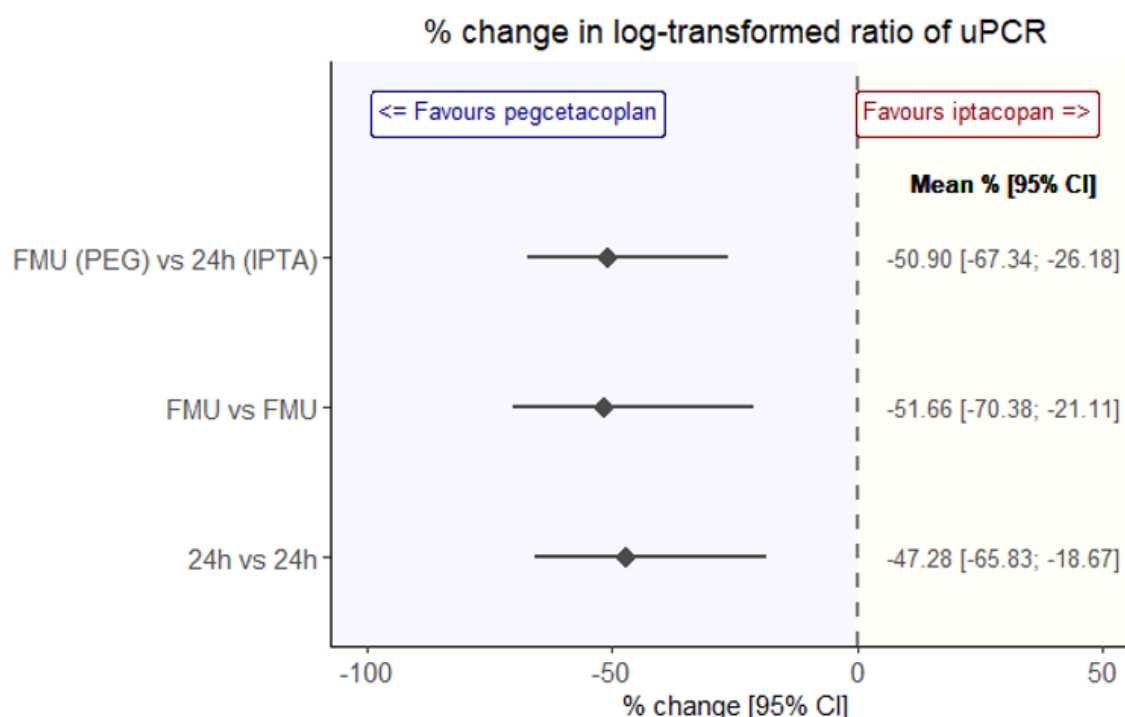
Outcome	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
log(UPCR/UPCR baseline), mean %[95% CI]			

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UPCR FMU vs. FMU	-68.1 [-76.2; -57.3]	-34.1 [-55.5; -2.4]	-51.66 [-70.38; -21.11]
UPCR FMU vs. 24h		-35.1 [-51.1; -13.8]	-50.90 [-67.34; -26.18]
UPCR 24h vs. 24h	-65.8 [-75.4; -52.5]	-35.1 [-51.1; -13.8]	-47.28 [-65.83; -18.67]
UPCR thresholds (FMU vs 24h), risk difference [95% CI]			
≥3 (g/g)	-0.09 [-0.22; 0.05]	-0.10 [-0.32; 0.12]	0.01 [-0.24; 0.27]
1-3 (g/g)	-0.21 [-0.38; -0.04]	0.02 [-0.20; 0.25]	-0.23 [-0.51; 0.05]
<1 (g/g)	0.31 [0.15; 0.47]	0.05 [-0.07; 0.17]	0.26 [0.06; 0.46]
≥50% reduction	0.53 [0.29; 0.76]	0.23 [0.07; 0.40]	0.29 [0.01; 0.58]
UPCR thresholds (FMU vs 24h), odds ratio [95% CI]			
≥3 (g/g)	0.56 [0.22; 1.41]	0.65 [0.25; 1.67]	0.87 [0.23; 3.26]
1-3 (g/g)	0.42 [0.20; 0.87]	1.11 [0.44; 2.76]	0.38 [0.12; 1.22]
<1 (g/g)	4.22 [1.89; 9.40]	2.00 [0.34; 11.66]	2.11 [0.30; 14.61]
≥50% reduction	30.90 [8.39; 113.77]	6.93 [1.41; 33.93]	4.46 [0.57; 34.84]

Abbreviations: 24h, 24-hour urine collection, C3G, complement 3 glomerulopathy, CI, confidence interval, FMU, first-morning spot urine sample, IPTA – iptacopan, PEG – pegcetacoplan, UPCR – urine protein-to-creatinine ratio.

Figure 15. Comparison of log (UPCR) percent change from baseline between pegcetacoplan and iptacopan.



Abbreviations: 24h – 24-hour urine collection, All – all VALIANT patients, C3G – VALIANT patients with C3G disease, CI – confidence interval, FMU – first morning urine, IPTA – iptacopan, PEG – pegcetacoplan, UPCR – urine protein-to-creatinine ratio.

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There was no evidence for significant differences between pegcetacoplan and iptacoplan regarding the other proteinuria-related outcomes (proportion of patients with UPCR ranging between 1-3 g/g, proportion of patients with UPCR ≥ 3 g/g).

2.10.2.2 Renal function

APPEAR-C3G reported two estimates for the mean change from baseline in eGFR. Both estimates were assessed using MMRM models, one with the baseline eGFR, and the second with baseline eGFR and baseline log(UPCR) as explanatory variables. The MMRM estimate reported in VALIANT with model including baseline eGFR was compared with both estimates from APPEAR-C3G. The difference in both estimates of change from baseline in eGFR numerically favoured pegcetacoplan compared to iptacoplan but with no significant differences (MD = 4.16 [-3.45; 11.76]) (Table 46 , Figure 16).

The difference in eGFR stabilisation and achieving the composite renal endpoint numerically favoured pegcetacoplan compared to iptacoplan, but without statistically significant differences (RD = 0.09 [-0.13; 0.31] and 0.22 [-0.07; 0.52], respectively) (Table 46).

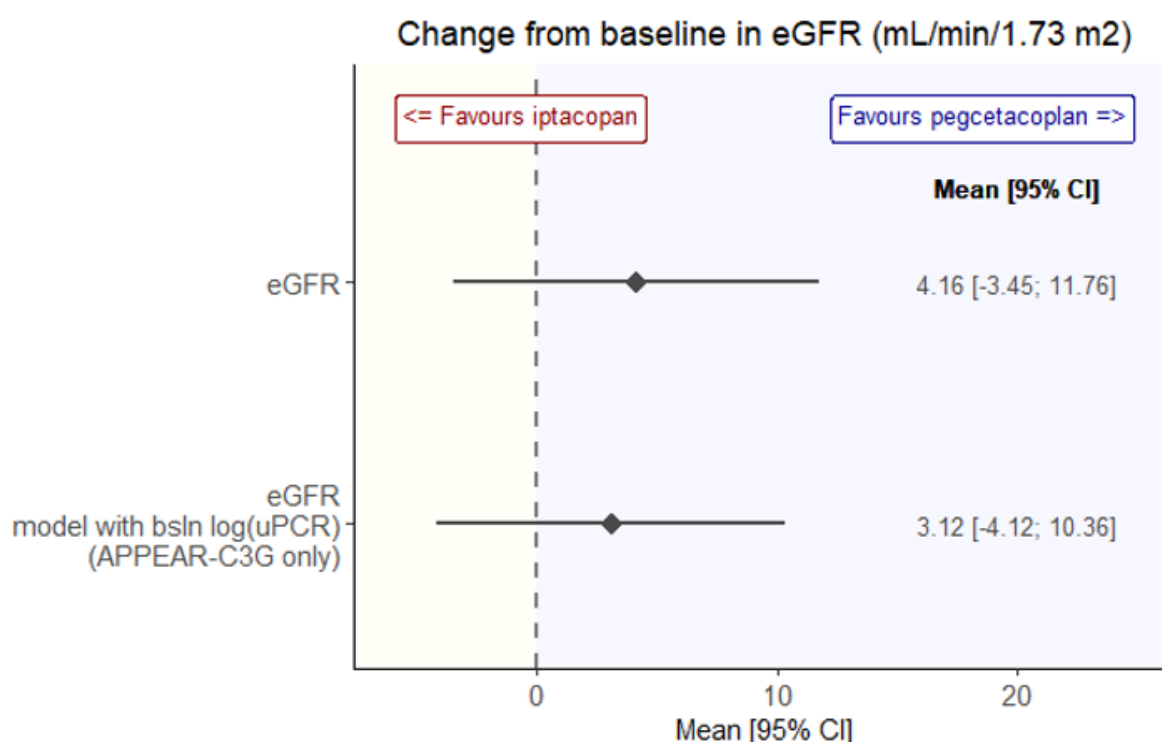
Table 46. Results of Bucher's indirect comparison between Pegcetacoplan and Iptacoplan for outcomes related to renal function.

Characteristics	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) vs VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
Change from baseline, mean [95% CI]			
eGFR (mL/min/1.73 m ²)	6.31 [0.50; 12.12]	2.156 [-2.75; 7.06] 3.19* [-1.13; 7.51]	4.16 [-3.45; 11.76] 3.12 [-4.12; 10.36]
Risk difference [95% CI]			
Composite renal endpoint	0.46 [0.21; 0.70]	0.23 [0.07; 0.40]	0.22 [-0.07; 0.52]
Stable eGFR ($\leq 15\%$ reduction)	0.09 [-0.08; 0.26]	0.01 [-0.14; 0.15]	0.09 [-0.13; 0.31]
Odds ratio [95% CI]			
Composite renal endpoint	27.48 [6.10; 123.85]	7.15 [1.43; 35.72]	3.85 [0.42; 34.84]
Stable eGFR ($\leq 15\%$ reduction)	1.49 [0.72; 3.12]	1.06 [0.24; 4.61]	1.41 [0.27; 7.26]

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Abbreviations: C3G – complement 3 glomerulopathy, CI – confidence interval, eGFR – estimated glomerular filtration rate, IPTA – iptacopan, PEG – pegcetacoplan. * model including baseline eGFR and log(UPCR) as covariates in APPEAR-C3G.

Figure 16. Comparison of eGFR change from baseline between pegcetacoplan and Iptacopan



Abbreviations: All – all VALIANT patients, C3G – VALIANT patients with C3G disease, CI – confidence interval, FMU – first morning urine, IPTA – iptacopan, PEG – pegcetacoplan, UPCR – urine protein-to-creatinine ratio.

2.10.2.3 Histological outcome

In both trials the mean change from baseline in C3G histologic disease activity total score was assessed using ANCOVA model including the baseline value of the endpoint.

The point estimates were comparable between pegcetacoplan and iptacopan with no significant differences (MD = -0.17 [-2.25; 1.91]) (Table 47 and Figure 17). As mentioned previously, this outcome was not originally designed to be a predictor of C3G disease progression at diagnosis and was not meant to measure changes between two time points, calling into question the utility of this endpoint in the context of longitudinal treatment effects.

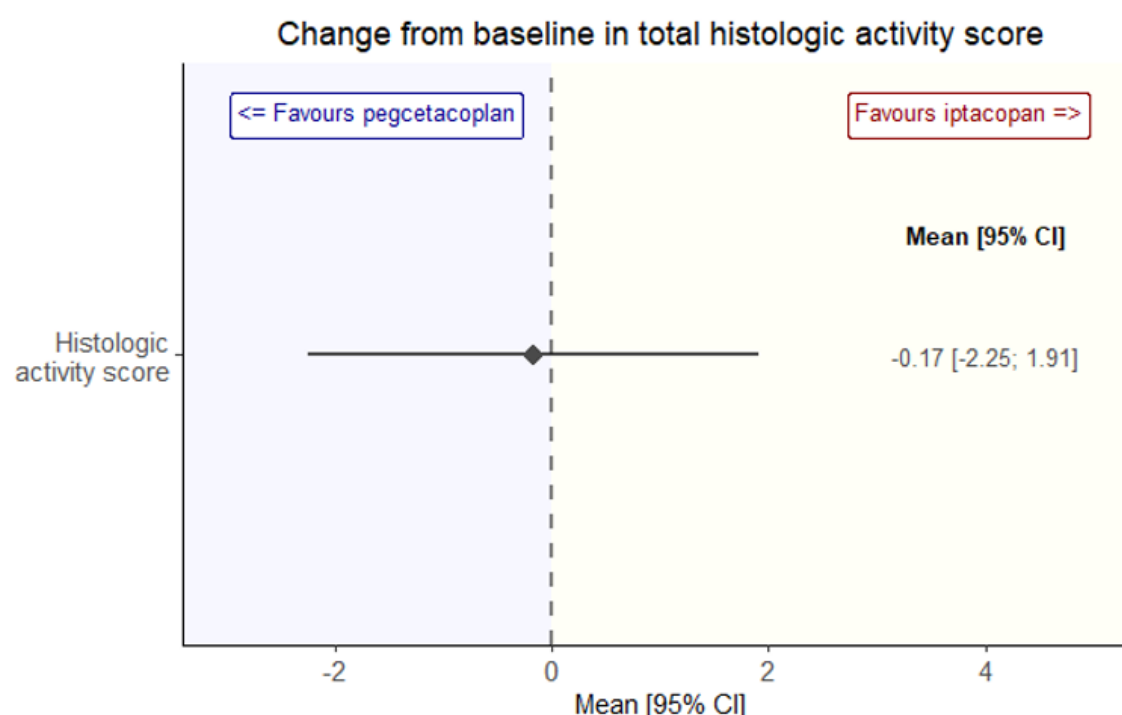
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Table 47. Results of Bucher's indirect comparison between Pegcetacoplan and Iptacopan for the C3G histologic index activity Total score.

Characteristics	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
Change from baseline, mean [95% CI]			
Total histologic activity score	-1.00 [-2.80; 0.80]	-0.833 [-1.87, 0.20]	-0.17 [-2.25; 1.91]

Abbreviations: C3G – complement 3 glomerulopathy, CI – confidence interval, IPTA – iptacopan, PEG – pegcetacoplan.

Figure 17. Comparison of C3G histologic index activity Total score change from baseline between pegcetacoplan and Iptacopan



Abbreviations: All – all VALIANT patients, C3G – VALIANT patients with C3G disease, CI – confidence interval, IPTA – iptacopan, PEG – pegcetacoplan

2.10.2.4 Change from baseline in FACIT-Fatigue score

Both trials reported the change from baseline in FACIT-Fatigue assessed using ANCOVA model including the baseline value as a covariate.

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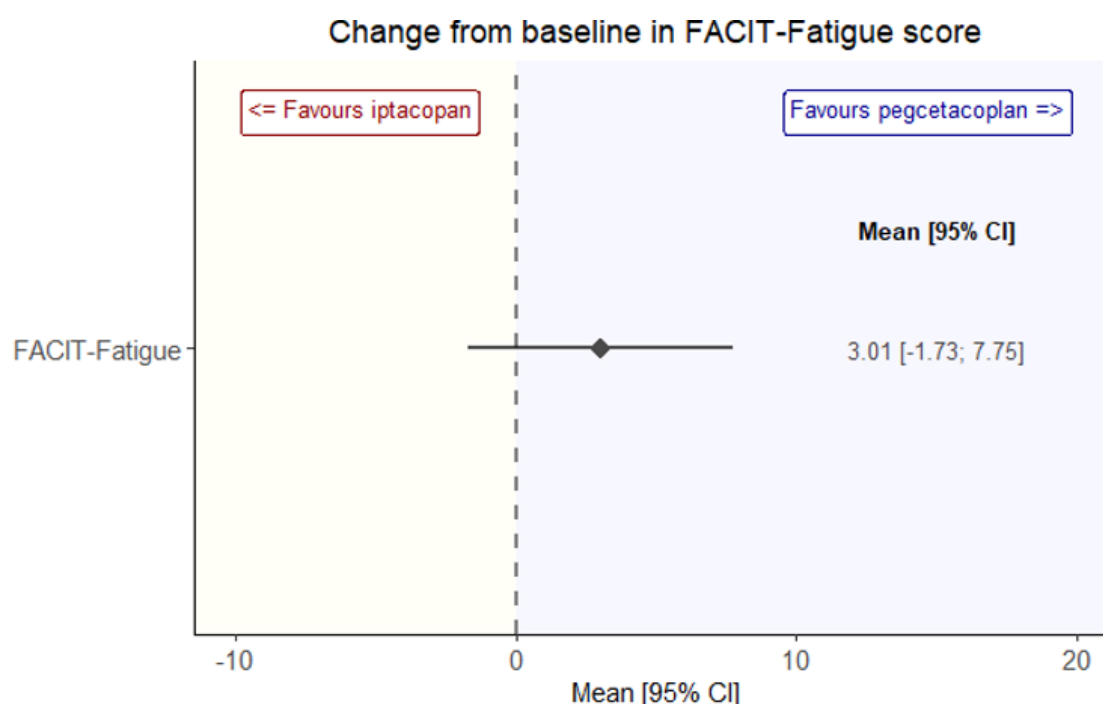
Although there was a numerical difference favouring pegcetacoplan in terms of the FACIT-Fatigue score, Bucher's comparison did not find any significant differences between pegcetacoplan and iptacoplan in the FACIT-Fatigue score (MD = 3.01 [-1.73; 7.75]) (Table 48, Figure 18).

Table 48. Results of Bucher's indirect comparison between pegcetacoplan and Iptacoplan regarding the FACIT-Fatigue score.

Characteristics	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
Change from baseline, mean [95% CI]			
FACIT-Fatigue score	0.41 [-2.86; 3.68]	-2.598 [-6.03, 0.84]	3.01 [-1.73; 7.75]

Abbreviations: C3G – complement 3 glomerulopathy, CI – confidence interval, FACIT-Fatigue – Functional Assessment of Chronic Illness Therapy - Fatigue, IPTA – iptacoplan, PEG – pegcetacoplan.

Figure 18. Comparison of FACIT-Fatigue change from baseline between Pegcetacoplan and Iptacoplan



Abbreviations: All – all VALIANT patients, C3G – VALIANT patients with C3G disease, CI – confidence interval, FACIT-Fatigue – Functional Assessment of Chronic Illness Therapy - Fatigue, IPTA – iptacoplan, PEG – pegcetacoplan.

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2.10.2.5 Subgroup analysis

Given the differences in eligibility criteria between trials, the robustness of the ITC was evaluated across VALIANT subgroups based on eligibility criteria differences: underlying disease (C3G, IC-MPGN), age (adults, adolescents), sex (male, female), serum C3 levels (<77 mg/dL, ≥77 mg/dL), and combinations (adults with C3G, serum C3 <77 mg/dL, and both). The subgroup differences between pegcetacoplan and placebo were then compared to the overall estimates from the APPEAR-C3G trial. The results are presented in Appendix C and summarised below.

Proteinuria

Mean percent change in uPCR (FMU vs. 24 h) from baseline

Pegcetacoplan was associated with a significantly greater reduction in UPCR compared to placebo in the overall VALIANT trial population, as well as in all analysed subgroups. The only significant interaction was observed for baseline serum C3 levels, suggesting that patients with serum C3 levels <77 mg/dL exhibit a significantly stronger response to pegcetacoplan (Appendix C, Figure 34).

Pegcetacoplan was significantly superior to iptacopan in reducing UPCR from baseline when stratifying by disease type (C3G vs. IC-MPGN), age (adults vs. adolescents) and sex (Appendix C, Figure 34).

Proportion of patients achieving <1 g/g UPCR (FMU vs. 24h)

Pegcetacoplan was associated with a significantly higher probability of achieving a reduction of UPCR below 1 g/g and this was generally consistent across all subgroups, including adult patients with C3G and those with baseline serum C3 level <77 mg/dL (RD = 0.51 [0.18; 0.84]) which was the most comparable population to APPEAR-C3G trial (Appendix C; Figure 36).

The superiority of pegcetacoplan over iptacopan observed in the overall population (RD = 0.26 [0.06; 0.46]) was also evident in key subgroups, including patients with C3G (RD = 0.26 [0.04; 0.48]), adults (RD = 0.32 [0.07; 0.56]), and those with baseline C3 levels <77 mg/dL (RD = 0.38 [0.15; 0.60]). This superiority was also found in the subgroup combining these characteristics, which closely aligns with the

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population recruited in the APPEAR-C3G trial (adults with C3G and serum C3 levels <77 mg/dL, RD = 0.46 [0.11; 0.82]) Appendix C, Figure 36).

Renal function

Pegcetacoplan was associated with a significantly greater preservation of eGFR compared to placebo in the overall VALIANT trial population (MD = 6.31 [0.50; 12.12]). This effect was consistent across most subgroups in terms of point estimates, though confidence intervals crossed the threshold for statistical significance. The only significant interaction was observed for baseline serum C3 levels, indicating that patients with serum C3 <77 mg/dL demonstrated a markedly stronger response to pegcetacoplan versus those with ≥ 77 mg/dL (MD = 10.71 vs. 0.91, $p = 0.0345$) (Appendix C; Figure 38).

Sub-group analyses did not find any significant differences between pegcetacoplan and iptacoplan in the change from baseline in eGFR in any sub-group population but all favoured pegcetacoplan (Appendix C; Figure 39).

2.10.3 Summary of results

The comparable efficacy of pegcetacoplan was evaluated based on two pivotal trials: VALIANT for pegcetacoplan and APPEAR-C3G for iptacoplan. Compared to placebo groups, both treatments significantly reduced proteinuria, measured as the percentage reduction in log(UPCR) from baseline (by 68.1% vs. 35.1% for pegcetacoplan and iptacoplan, respectively), and increased the likelihood of achieving a $\geq 50\%$ reduction in proteinuria (OR = 30.90 vs. 6.93 for pegcetacoplan and iptacoplan, respectively). Additionally, pegcetacoplan improved the odds of achieving UPCR <1 g/g and halted eGFR decline compared with placebo. Both treatments also increased the proportion of patients achieving a composite renal endpoint, defined as stable eGFR and a $\geq 50\%$ reduction in UPCR (OR = 27.48 vs. 7.15 for pegcetacoplan and iptacoplan, respectively).

The comparison between pegcetacoplan and iptacoplan was conducted using Bucher's indirect comparison, a standard method for evaluating treatments studied

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against the same reference arm (114). When applied to two independent trials without additional treatment loops, Bucher's approach provides results consistent with more sophisticated methodologies, such as Bayesian network meta-analysis (NMA), while offering greater simplicity and transparency.

The results from Bucher's indirect comparison indicated that:

- pegcetacoplan was associated with a significantly greater reduction in UPCR from baseline compared to iptacopan.
- pegcetacoplan had a significantly higher probability of achieving a $\geq 50\%$ reduction in UPCR and UPCR < 1 g/g.
- difference in eGFR stabilisation and change from baseline in eGFR favoured pegcetacoplan compared to iptacopan numerically but with no significant differences.
- no significant differences were observed for histological outcomes or FACIT Fatigue score assessments (although the numerical difference favoured pegcetacoplan).

2.10.4 Uncertainties in the indirect and mixed treatment comparisons

Both trials were placebo-controlled and similarly designed, but there were key differences in inclusion criteria. VALIANT included patients with C3G and IC-MPGN, adults and adolescents, and native and post-transplant kidneys, whereas APPEAR-C3G included only adult patients with C3G, serum C3 levels < 77 mg/ml, and native kidneys. These differences have the potential to pose limitations to the Bucher's analysis, which assumes comparability between trial populations without significant differences in effect modifiers. To address this, the efficacy of pegcetacoplan was assessed in sensitivity analyses across subgroups based on disease type, age, sex, and serum C3 levels.

The sensitivity analyses demonstrated that pegcetacoplan consistently improved proteinuria and prevented eGFR decline across all patient subgroups. Notably:

- Underlying disease (C3G vs. IC-MPGN) and age (adults vs. adolescents) had no impact on pegcetacoplan benefits.

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- Baseline serum C3 level emerged as a potential effect modifier. In patients with C3 <77 mg/dL (the inclusion criterion for APPEAR-C3G), pegcetacoplan demonstrated significantly stronger efficacy in reducing proteinuria and preventing eGFR decline over placebo than their counterparts with serum C3 ≥77 mg/dL.

Based on these sensitivity findings, the broader inclusion criteria of the VALIANT trial make it more representative of the general patient population, enhancing its external validity. This suggests that the outcomes observed in VALIANT are more likely to be replicated in real world clinical practice. In contrast, APPEAR-C3G's narrower inclusion criteria may have optimised conditions for demonstrating the efficacy of iptacoplan but limit its generalisability. By restricting the study population to a subset of patients with serum C3 levels <77 mg/dL—those most likely to respond—APPEAR-C3G introduces significant selection bias. This makes it challenging to predict the real-world effectiveness of iptacoplan, particularly when administered to less favourable patient populations, such as those with normal serum C3 levels.

2.11 Adverse reactions

2.11.1 VALIANT Adverse events

Adverse events (AEs) were reported as the number of participants who reported the event at least once (n) as well as the total events count (m). If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m).

Table 49 provides an overview of AEs experienced during the RCP. The number of participants who had a TEAE during the RCP was similar. Fifty-three (84.1%) participants in the pegcetacoplan group and 57 (93.4%) participants in the placebo group reported TEAEs. Most patients experienced TEAEs that were mild or moderate in severity, with no difference in the number of serious TEAEs between the pegcetacoplan group (6; 9.5%) and placebo group (6; 9.8%).

The number of participants who had a TEAE that led to treatment discontinuation was the same between groups: pegcetacoplan: 2 (3.2%), placebo 2 (3.3%). The

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number of participants with a dose interruption due to a TEAE was lower in the pegcetacoplan group compared to the placebo group: 7 (11.1%) vs 12 (19.7%), respectively.

The number of participants who had a TEAE that led to study discontinuation was the same: 1 (1.6%) participant in the pegcetacoplan group and 1 (1.6%) participant in the placebo group.

The proportion of participants with infusion-related TEAEs was slightly higher in the pegcetacoplan group (33.3%) compared with the placebo group (26.2%). Infusion site reactions were similar. No rejection episodes or graft loss were reported in the post-transplant participants.

The number of participants who had a treatment-related TEAE was similar: 25 (39.7%) participants in the pegcetacoplan group and 26 (42.6%) participants in the placebo group.

There was 1 death because of respiratory failure due to COVID-19 pneumonia in the pegcetacoplan group which was considered not to be related to study treatment. Additionally, no serious cases of infection by encapsulated bacteria were reported during the RCP.

Table 49: Overview of Adverse Events During the RCP (Safety Set)

Characteristics	Pegcetacoplan (N = 63) n (%) m	Placebo (N = 61) n (%) m	Overall (N = 124) n (%) m
Any TEAE	53 (84.1) 390	57 (93.4) 380	110 (88.7) 770
Treatment-related TEAE	25 (39.7) 125	26 (42.6) 134	51 (41.1) 259
Infusion-related TEAEs	21 (33.3) 110	16 (26.2) 124	37 (29.8) 234
Serious TEAE	6 (9.5) 9	6 (9.8) 10	12 (9.7) 19
Maximum severity of TEAEs			
Mild	27 (42.9)	26 (42.6)	53 (42.7)
Moderate	23 (36.5)	27 (44.3)	50 (40.3)
Severe	3 (4.8)	4 (6.6)	7 (5.6)
Infusion site reaction	18 (28.6) 103	17 (27.9) 121	35 (28.2) 224
TEAE leading to treatment withdrawn	2 (3.2) 2	2 (3.3) 2	4 (3.2) 4
TEAE leading to dose interruption	7 (11.1) 13	12 (19.7) 29	19 (15.3) 42
TEAE leading to study discontinuation	1 (1.6) 1	1 (1.6) 1	2 (1.6) 2

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Characteristics	Pegcetacoplan (N = 63) n (%) m	Placebo (N = 61) n (%) m	Overall (N = 124) n (%) m
TEAE leading to death	1 (1.6) 1	0	1 (0.8) 1
Rejection episodes	0	0	0
Graft loss	0		

Abbreviation: m, number of events; n, number of participants; TEAE, treatment-emergent adverse event. Notes: A TEAE was defined as any new adverse event that began, or any pre-existing condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences were counted in the total events count. A treatment-related AE was defined as a TEAE with a relationship to study drug or definitely related, or possibly related. Any AEs with missing or unknown relationship was considered as related to study drug. Rejection episodes and graft loss were summarised for posttransplant participant only. Percentage will be based on post-transplant participant.

2.11.1.1 Commonly reported AEs

Commonly reported TEAEs (experienced by ≥ 3 individuals) during the RCP are listed in Table 50. The most frequently reported ($\geq 40\%$) TEAEs included infections and infestations (pegcetacoplan: 35 [55.6%]; placebo: 27 [44.3%]), and general disorders and administration site conditions (pegcetacoplan: 29 [46.0%]; placebo: 29 [47.5%]). The most commonly reported TEAEs ($\geq 10\%$) in either group (pegcetacoplan vs placebo) were pyrexia (19.0% vs 9.8%), nasopharyngitis (17.5% vs 11.5%), headache (12.7% vs 16.4%) and vomiting (7.9% vs 13.1%).

Table 50: Summary of common TEAEs (experienced by ≥ 3 participants in either treatment group) during the RCP (Safety Set)

System Organ Class Preferred Term	Pegcetacoplan (N = 63)	Placebo (N = 61)
Any TEAE n (%) m	53 (84.1) 390	57 (93.4) 380
Infections and infestations, n (%)	35 (55.6)	27 (44.3)
Nasopharyngitis	11 (17.5)	7 (11.5)
Influenza	7 (11.1)	3 (4.9)
Upper respiratory tract infection	4 (6.3)	5 (8.2)
COVID-19	2 (3.2)	4 (6.6)
Gastroenteritis	2 (3.2)	3 (4.9)
Herpes zoster	0	3 (4.9)
General disorders and administration site conditions, n (%)	29 (46.0)	29 (47.5)
Pyrexia	12 (19.0)	6 (9.8)
Fatigue	4 (6.3)	1 (1.6)
Infusion site erythema	3 (4.8)	0
Injection site pruritus	3 (4.8)	1 (1.6)

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Oedema	3 (4.8)	5 (8.2)
Oedema peripheral	3 (4.8)	3 (4.9)
Injection site pain	2 (3.2)	5 (8.2)
Injection site swelling	2 (3.2)	6 (9.8)
Asthenia	0	3 (4.9)
Infusion site pain	0	3 (4.9)
Gastrointestinal disorders, n (%)	19 (30.2)	17 (27.9)
Nausea	6 (9.5)	4 (6.6)
Vomiting	5 (7.9)	8 (13.1)
Abdominal pain	4 (6.3)	4 (6.6)
Abdominal pain upper	3 (4.8)	2 (3.3)
Dyspepsia	3 (4.8)	0
Diarrhoea	2 (3.2)	7 (11.5)
Respiratory, thoracic and mediastinal disorders, n (%)	12 (19.0)	9 (14.8)
Cough	6 (9.5)	1 (1.6)
Oropharyngeal pain	3 (4.8)	3 (4.9)
Rhinorrhoea	3 (4.8)	2 (3.3)
Skin and subcutaneous tissue disorders, n (%)	12 (19.0)	10 (16.4)
Acne	0	4 (6.6)
Nervous system disorders, n (%)	10 (15.9)	13 (21.3)
Headache	8 (12.7)	10 (16.4)
Dizziness	0	6 (9.8)
Injury, poisoning and procedural complications, n (%)	8 (12.7)	7 (11.5)
Contusion	5 (7.9)	2 (3.3)
Investigations	8 (12.7)	13 (21.3)
Blood creatine phosphokinase increased	3 (4.8)	2 (3.3)
Blood cholesterol increased	0	3 (4.9)
Musculoskeletal and connective tissue disorders, n (%)	8 (12.7)	8 (13.1)
Muscle spasms	0	3 (4.9)
Renal and urinary disorders, n (%)	7 (11.1)	12 (19.7)
Acute kidney injury	4 (6.3)	2 (3.3)
Vascular disorders, n (%)	7 (11.1)	5 (8.2)
Hypertension	4 (6.3)	5 (8.2)
Blood and lymphatic system disorders, N (%)	5 (7.9)	7 (11.5)
Anaemia	0	4 (6.6)

Abbreviations: n = number of participants; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event. Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Adverse events were coded to SOC and PT using MedDRA Version 26.0

2.11.1.2 Treatment-related AEs

Treatment-related TEAEs experienced by ≥ 3 participants for the RCP (safety set) are listed in Table 51. A treatment-related AE was defined as a TEAE with a relationship to study drug; definitely related, possibly related, or not reported.

Table 51: Treatment-Related TEAEs (experienced by ≥ 3 participants) in either treatment group) during the RCP (Safety Set)

System Organ Class Preferred Term	Pegcetacoplan (N = 63) n (%)	Placebo (N = 61) n (%)
Any TEAE, n (%), m	25 (39.7) 125	26 (42.6) 134
General disorders and site conditions	18 (28.6)	13 (21.3)
Pyrexia	4 (6.3)	0
Injection site pruritus	3 (4.8)	1 (1.6)
Injection site pain	2 (3.2)	5 (8.2)
Injection site swelling	2 (3.2)	4 (6.6)
Infusion site pain	0	3 (4.9)
Nervous system disorders	3 (4.8)	4 (6.6)
Headache	3 (4.8)	3 (4.9)

Abbreviations: m = number of events; n = number of participants; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event. Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Adverse events were coded to SOC and PT using MedDRA Version 26.0.

The most frequently reported treatment-related TEAEs (reported by $\geq 10\%$ of participants) included general disorders and administration site conditions (pegcetacoplan: 18 [28.6%]; placebo: 13 [21.3%]) and infections and infestations (pegcetacoplan: 7 [11.1%]; placebo: 7 [11.5%]). The most commonly reported treatment-related TEAEs (reported by $\geq 5\%$ of participants) in either group (pegcetacoplan vs placebo) were pyrexia (6.3% vs 0%), injection site pain (3.2% vs 8.2%), and injection site swelling (3.2% vs 6.6%).

During the RCP, the treatment-related TEAE reported by $\geq 5\%$ of participants in the pegcetacoplan group and that was reported by more pegcetacoplan participants than placebo participants was pyrexia (pegcetacoplan: 6.3% vs placebo: 0%).

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Table 52 shows infusion-related TEAEs experienced by ≥ 2 participants during the RCP (safety set). Infusion-related TEAEs include those PTs that were reported by participants who were considered to be related to the infusion procedure based on the investigator assessment.

Table 52: Infusion-related TEAEs (experienced by ≥ 2 participants in either treatment group) during the RCP (Safety Set)

System Organ Class Preferred Term	Pegcetacoplan (N = 63)	Placebo (N = 61)
Any TEAE, n (%) m	21 (33.3) 110	16 (26.2) 124
General disorders and administration site conditions, n (%)	17 (27.0)	15 (24.6)
Infusion site erythema	3 (4.8)	0
Injection site pruritus	3 (4.8)	1 (1.6)
Infusion site pruritus	2 (3.2)	0
Injection site erythema	2 (3.2)	1 (1.6)
Injection site pain	2 (3.2)	5 (8.2)
Injection site reaction	2 (3.2)	0
Injection site swelling	2 (3.2)	6 (9.8)
Administration site pain	0	2 (3.3)
Infusion site pain	0	3 (4.9)
Injury, poisoning and procedural complications, n (%)	3 (4.8)	3 (4.9)
Contusion	2 (3.2)	2 (3.3)

Abbreviations: n = number of participants; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event. Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Adverse events were coded to SOC and PT using MedDRA Version 26.0

Table 53 shows infusion site reaction TEAEs experienced by ≥ 2 participants for the RCP (safety set). Infusion site reaction TEAEs were reported by 18 participants (28.6%) in the pegcetacoplan group and 17 participants (27.9%) in the placebo group. Most infusion site reaction TEAEs (those reported by $\geq 10\%$ of participants) were in the SOC of general disorders and administration site conditions SOC (16 [25.4%] participants in the pegcetacoplan group vs 16 [26.2%] participants in the placebo group). The most commonly reported infusion site reaction TEAE by PT (those reported by $\geq 5\%$ of participants) in either group (pegcetacoplan vs placebo) was injection site swelling (3.2% vs 9.8%). During the RCP, there were no infusion

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site reaction TEAE that were reported by $\geq 5\%$ of participants in the pegcetacoplan group and that were reported by more pegcetacoplan participants than placebo participants.

Table 53: Infusion site reaction TEAEs (experienced by ≥ 2 participants in either treatment group) during the RCP (Safety Set)

System Organ Class Preferred Term	Pegcetacoplan (N = 63)	Placebo (N = 61)
Any TEAE, n (%) m	18 (28.6) 103	17 (27.9) 121
General disorders and administration site conditions, n (%)	16 (25.4)	16 (26.2)
Infusion site erythema	3 (4.8)	0
Injection site pruritus	3 (4.8)	1 (1.6)
Infusion site pruritus	2 (3.2)	0
Injection site erythema	2 (3.2)	1 (1.6)
Injection site reaction	2 (3.2)	0
Injection site swelling	2 (3.2)	6 (9.8)
Infusion site reaction	1 (1.6)	2 (3.3)
Injection site pain	1 (1.6)	4 (6.6)
Administration site pain	0	2 (3.3)
Infusion site pain	0	3 (4.9)

Abbreviations: n = number of participants; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event. Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Adverse events were coded to SOC and PT using MedDRA Version 26.0.

2.11.1.3 Deaths, SAEs and other significant AEs

There was one death reported during the RCP. A 62-year-old White male participant (participant 49002001) in the pegcetacoplan group, with a history of chronic obstructive pulmonary disease and diabetes mellitus, was diagnosed with COVID-19 pneumonia and respiratory failure on 20 December 2023 (day 195) and subsequently died 9 days later of respiratory failure due to COVID-19 pneumonia (end date 29 December 2023 [day 204]). Both events were severe SAEs requiring hospitalisation, which were considered to be unrelated to study treatment. Study drug was withdrawn due to the event of respiratory failure. Chronic obstructive pulmonary disease and use of immunosuppressants was assessed as the likely

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cofounders leading towards the development of COVID-19 pneumonia and the subsequent respiratory failure.

A summary of serious TEAEs by PT during the RCP (safety set) is presented in Table 54. In total, 12 participants had a serious TEAE during the RCP: 6 (9.5%) participants with 9 events in the pegcetacoplan group and 6 (9.8%) participants with 10 events in the placebo group. The most common serious TEAE was acute kidney injury, which was reported by 1 participant in the pegcetacoplan group and 2 participants in the placebo group. No other specific serious TEAE was experienced by more than 1 participant. One participant in the pegcetacoplan group had a serious TEAE (pyrexia) that was considered to be related to study drug by the investigator. No other treatment-related serious TEAEs were reported.

Table 54: Serious TEAEs during the RCP (Safety Set)

System Organ Class Preferred Term	Pegcetacoplan N = 63 n (%)	Placebo N = 61 n (%)
Any serious TEAEs, n (%), m	6 (9.5) 9	6 (9.8) 10
Infections and infestations, n (%)	3 (4.8)	1 (1.6)
COVID-19 pneumonia	1 (1.6)	0
Influenza	1 (1.6)	0
Pneumonia	1 (1.6)	0
Viral infection	0	1 (1.6)
Renal and urinary disorders, n (%)	2 (3.2)	4 (6.6)
Acute kidney injury	1 (1.6)	2 (3.3)
Nephrotic syndrome	1 (1.6)	0
Proteinuria	0	1 (1.6)
Tubulointerstitial nephritis	0	1 (1.6)
General disorders and administration site conditions, n (%)	1 (1.6)	0
Pyrexia	1 (1.6)	0
Respiratory, thoracic and mediastinal disorders, n (%)	1 (1.6)	0
Respiratory failure	1 (1.6)	0
Vascular disorders	1 (1.6)	0
Hypertension	1 (1.6)	0
Gastrointestinal disorders	0	1 (1.6)
Vomiting	0	1 (1.6)
Investigations, n (%)	0	1 (1.6)
Blood creatinine increased	0	1 (1.6)
Pregnancy, puerperium and perinatal conditions	0	1 (1.6)

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System Organ Class Preferred Term	Pegcetacoplan N = 63 n (%)	Placebo N = 61 n (%)
Abortion spontaneous	0	1 (1.6)
Pregnancy	0	1 (1.6)

Abbreviations: n = number of participants; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event. Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Adverse events were coded to System Organ Class and Preferred Term using MedDRA Version 26.0

2.11.2 VALE adverse events

The analyses of the long-term safety of pegcetacoplan were performed using the VALE safety set and the re-aligned safety set. The latter includes all participants who received a dose of pegcetacoplan in VALIANT. Safety variables include AEs, SAEs, deaths, kidney transplant rejection episodes, and kidney transplant graft loss

An overall summary of TEAEs is presented in Table 55 based on the re-aligned safety set. A total of 94 (78.3%) of 120 participants had at least 1 TEAE after starting pegcetacoplan in VALIANT. There was 1 death during VALIANT because of respiratory failure due to COVID-19 pneumonia in the pegcetacoplan group, which was considered to be not related to study treatment. There were no deaths during pegcetacoplan treatment in VALE. In the combined studies, the maximum severity of TEAEs was mild in 45 (37.5%) participants, moderate in 40 (33.3%) participants, and severe in 9 (7.5%) participants. A total of 49 (40.8%) participants experienced 105 unique treatment-related TEAEs. A total of 37 (30.8%) participants experienced 63 unique infusion-related TEAEs. Infusion-site reactions occurred in 35 (29.2%) participants, and 59 unique serious TEAEs occurred. Two (1.7%) participants had a TEAE that led to treatment discontinuation.

Table 55: Overall Summary of TEAEs – Combined Analysis (Re-Aligned Safety Set)

Events		VALIANT^e (N=120)	VALE^f (N=53)	Combined (N=120)
All TEAEs ^{a,b}	Number of participants, n (%)	91 (75.8)	30 (56.6)	94 (78.3)
	Total events, n	726	125	851

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	Unique events, n	467	66	522
Pegcetacoplan-related TEAE ^c	Number of participants, n (%)	44 (36.7)	10 (18.9)	49 (40.8)
	Total events, n	271	70	341
	Unique events, n	94	14	105
Infusion-related TEAEs	Number of participants, n (%)	34 (28.3)	6 (11.3)	37 (30.8)
	Total events, n	226	65	291
	Unique events, n	56	10	63
Serious TEAE	Number of participants, n (%)	11 (9.2)	1 (1.9)	12 (10.0)
	Total events, n	23	2	25
	Unique events, n	20	2	22
Maximum severity of TEAEs	Mild, n (%)	47 (39.2)	19 (35.8)	45 (37.5)
	Moderate	36 (30.0)	10 (18.9)	40 (33.3)
	Severe	8 (6.7)	1 (1.9)	9 (7.5)
Infusion site reaction	Number of participants, n (%)	32 (26.7)	6 (11.3)	35 (29.2)
	Total events, n	227	65	292
	Unique events, n	52	10	59
TEAE leading to treatment withdrawn	Number of participants, n (%)	4 (3.3)	1 (1.9)	5 (4.2)
	Total events, n	4	1	5
	Unique events, n	4	1	5
TEAE leading to dose interruption	Number of participants, n (%)	17 (14.2)	0	17 (14.2)
	Total events, n	33	0	33
	Unique events, n	33	0	33
TEAE leading to study discontinuation	Number of participants, n (%)	2 (1.7)	0	2 (1.7)
	Total events, n	2	0	2
	Unique events, n	2	0	2
TEAE leading to death	Number of participants, n (%)	1 (0.8)	0	1 (0.8)
Rejection episodes ^d	Number of participants, n (%)	0	0	0
	Total events, n	0	0	0
Graft loss ^d	Number of participants, n (%)	0	0	0
	Total events, n	0	0	0

Abbreviations: n = number of evaluable participants; N = number of participants; TEAE = treatment-emergent adverse event. ^a TEAEs were defined as any new AEs that began, or any pre-existing condition that worsened in severity, after the first ever dose of study medication in either VALIANT or VALE and up to 56 days beyond the last dose of study drug. ^b If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences are counted in the total events count. ^c A treatment-related AE was defined as a TEAE with a Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

relationship to study drug of Definitely Related or Possibly Related. Any AEs with missing or unknown relationship were considered as related to study drug. ^d Rejection episodes and graft loss were summarised for posttransplant patients only. Percentages were based on post-transplant population. ^e Only TEAEs that occur in VALIANT and after the first dose of pegcetacoplan are summarised. ^f Only TEAEs that occur after the first dose of pegcetacoplan in VALE are summarised.

Exposure-adjusted incidence of TEAEs

Table 56 summarises the exposure-adjusted incidence of TEAEs for the participants. While for this interim analysis, the exposure for VALE is ~35% of that for VALIANT, the exposure-adjusted incidences of TEAEs between VALIANT and VALE did not increase.

Table 56: Exposure-adjusted incidence summary of TEAEs- combined analysis (re-aligned safety set)

Events	VALIANT ^d (N=120)		VALE ^d (N=120)		Combined (N=120)	
	EY	n (e)	EY	n (e)	EY	n (e)
All TEAEs ^{a,b}	24.6	91 (370.4)	15.5	30 (193.2)	27.3	94 (344.0)
Treatment-related TEAE ^c	57.7	44 (76.2)	24.5	10 (40.8)	70.7	49 (69.3)
Infusion-related TEAEs	63.5	34 (53.5)	26.1	6 (23.0)	77.9	37 (47.5)
Serious TEAE	78.4	11 (14.0)	28.8	1 (3.5)	98.1	12 (12.2)
Maximum severity of TEAEs						
Mild	56.5	47 (83.2)	21.5	19 (88.4)	72.7	45 (61.9)
Moderate	63.0	36 (57.1)	25.1	10 (39.9)	76.7	40 (52.2)
Severe	80.5	8 (9.9)	28.8	1 (3.5)	101.3	9 (8.9)
Infusion site reaction	65.	32 (48.7)	26.1	6 (23.0)	82.9	35 (42.2)
TEAE leading to treatment withdrawn	83.3	4 (4.8)	29.2	1 (3.4)	105.3	5 (4.7)
TEAE leading to dose interruption	75.8	17 (22.4)	29.3	0	95.9	17 (17.7)
TEAE leading to study discontinuation	84.0	2 (2.4)	29.3	0	106.5	2 (1.9)
TEAE leading to death	84.2	1 (1.2)	29.3	0	106.7	1 (0.9)
Rejection episodes ^d	84.4	0	29.3	0	106.9	0
Graft loss ^d	84.4	0	29.3	0	106.9	0

Abbreviations: AE = adverse event; e = number of events; EY = exposure years; n = number of evaluable participants; N = number of participants; TEAE = treatment-emergent adverse event. ^a TEAEs were defined as any new AEs that began, or any pre-existing condition that worsened in severity, after the first ever dose of study medication in either Study APL2-C3G-310 or Study APL2-C3G-314 and up to 56 days beyond the last dose of study drug. ^b If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences were counted in the total events count. ^c A treatment-related AE was defined as a TEAE with a relationship to study drug of Definitely Related or Possibly Related. Any AEs with missing or unknown relationship were considered as

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related to study drug. ^d Rejection episodes and graft loss were summarised for posttransplant patients only. Percentages were based on post-transplant patient population.

2.11.2.1 Commonly-reported AEs

Table 57 summarises the TEAEs experienced by $\geq 5\%$ of participants for the combined studies by SOC and PT for the re-aligned safety set. A total of 94 (78.3%) participants experienced a total of 851 events.

Overall, infections and infestations accounted for the most frequently reported SOC with 56 (46.7%) of the participants experiencing an event in this category, followed by general disorders and administration site conditions (43 [35.8%] participants), and gastrointestinal disorders (34 [28.3%] participants).

Table 57: TEAEs Experienced by $\geq 5\%$ of Participants by System Organ Class and Preferred Term - Combined Analysis (Re-Aligned Safety Set)

System Organ Class Preferred Term	Combined (N=120)
Any TEAE, n (%)	94 (78.3) 851
General disorders and administration site conditions, n (%)	43 (35.8)
Pyrexia	
Fatigue	16 (13.3)
Injection site erythema	7 (5.8)
Injection site swelling	6 (5.0)
Injection site pruritus	6 (5.0)
	5 (4.2)
Infections and infestations, n (%)	56 (46.7)
Nasopharyngitis	15 (12.5)
Influenza	10 (8.3)
Upper respiratory tract infection	9 (7.5)
COVID-19	6 (5.0)
Bronchitis	5 (4.2)
Skin and subcutaneous tissue disorders, n (%)	29 (24.2)
Pruritus	8 (6.7)
Gastrointestinal disorders, n (%)	34 (28.3)
Diarrhoea	11 (9.2)
Nausea	9 (7.5)
Vomiting	9 (7.5)
Abdominal pain	7 (5.8)
Abdominal pain upper	5 (4.2)
Nervous system disorders, n (%)	16 (13.3)
Headache	11 (9.2)

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Renal and urinary disorders, n (%)	16 (13.3)
Acute kidney injury	7 (5.8)
Vascular disorders, n (%)	16 (13.3)
Hypertension	8 (6.7)
Hypotension	6 (5.0)
Injury, poisoning and procedural complications, n (%)	15 (12.5)
Blood and lymphatic system disorders, n (%)	13 (10.8)
Respiratory, thoracic and mediastinal disorders, n (%)	20 (16.7)
Cough	8 (6.7)
Oropharyngeal pain	7 (5.8)
Metabolism and nutrition disorders, n (%)	19 (15.8)

Abbreviations: n = number of evaluable participants; N = number of participants; TEAE = treatment-emergent adverse event.

Table 58 summarises the TEAEs experienced by $\geq 5\%$ of participants for the combined studies in decreasing order by PT for the re-aligned safety set. The most frequently occurring PTs were pyrexia (16 [13.3] participants), nasopharyngitis (15 [12.5%]), diarrhoea (11 [9.2%] participants), headache (11 [9.2%] participants), and influenza (10 [8.3%] participants).

Table 58: TEAEs by Preferred Term Experienced by $\geq 5\%$ of Participants - Combined Analysis - Re-Aligned Safety Set

Preferred term	Combined (N=120)
Any TEAE ^{a,b} n (%) m	94 (78.3) 851
Pyrexia	16 (13.3)
Nasopharyngitis	15 (12.5)
Diarrhoea	11 (9.2)
Headache	11 (9.2)
Influenza	10 (8.3)
Nausea	9 (7.5)
Upper respiratory tract infection	9 (7.5)
Vomiting	9 (7.5)
Cough	8 (6.7)
Hypertension	8 (6.7)
Pruritus	8 (6.7)
Abdominal pain	7 (5.8)
Acute kidney injury	7 (5.8)
Fatigue	7 (5.8)
Oropharyngeal pain	7 (5.8)
COVID-19	6 (5.0)
Hypotension	6 (5.0)
Injection site erythema	6 (5.0)

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Injection site swelling	6 (5.0)

Abbreviations: AE = adverse event; n = number of evaluable participants; N = number of participants; TEAE = treatment-emergent adverse event. ^a TEAEs were defined as any new AEs that began, or any pre-existing condition that worsened in severity, after the first ever dose of study medication in either Study APL2-C3G-310 or Study APL2-C3G-314 and up to 56 days beyond the last dose of study drug. ^b If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Note: AEs were coded to System Organ Class and Preferred Term using MedDRA version 26.0.

2.11.2.2 Infusion-related TEAEs

In the combined studies, the most frequently occurring infusion-related TEAEs included the following PTs: injection site erythema (occurring in 6 [5.0%] participants), injection site swelling (6 [5.0%] participants), injection site pruritus (5 [4.2%] participants), infusion site swelling (4 [3.3%] participants), and infusion site erythema, infusion site pruritus, and injection site reaction (all occurring in 3 [2.5%] participants).

2.11.2.3 Deaths, SAEs and other significant AEs

In the combined studies, a total of 9 (7.5%) participants experienced severe TEAEs in the total population, with 45 (37.5%) participants in the mild category and 40 (33.3%) participants in the moderate category.

One (0.8%) death was reported during the VALIANT study. Cause of death was respiratory failure (due to COVID-19 pneumonia), assessed as not related to study drug by the investigator/sponsor. No deaths were reported during VALE.

As of the data cutoff date, only 1 (1.9%) of the 53 participants had experienced a SAE in this study; this participant reported SAEs of end stage renal disease and renal impairment, both assessed as not related to pegcetacoplan. A summary of SAEs for the re-aligned safety set is presented in Table 59. In the combined studies, 12 (10.0%) participants experienced treatment-emergent SAEs. The most frequently occurring SAEs were in the infections and infestations SOC (5 [4.2%] participants). None of the serious infections were reported during VALE as of the data cut; all serious infections occurred during the VALIANT study.

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Table 59: Serious TEAEs by System Organ Class and Preferred Term – Combined Analysis (Re-Aligned Safety Set)

Preferred Term	Combined (N=120)
Any TEAE ^{a,b} , n (%) m	12 (10.0) 25
Infections and infestations	5 (4.2)
COVID-19 pneumonia	1 (0.8)
Herpes zoster meningoencephalitis	1 (0.8)
Influenza	1 (0.8)
Pneumonia	1 (0.8)
Pneumonia streptococcal	1 (0.8)
Viral infection	1 (0.8)
Renal and urinary disorders	3 (2.5)
Acute kidney injury	2 (1.7)
End stage renal disease	1 (0.8)
Nephrotic syndrome	1 (0.8)
Renal impairment	1 (0.8)
General disorders and administration site conditions	2 (1.7)
Pyrexia	2 (1.7)
Injury, poisoning and procedural complications	2 (1.7)
Post procedural haematoma	1 (0.8)
Shunt malfunction	1 (0.8)
Metabolism and nutrition disorders	2 (1.7)
Dehydration	2 (1.7)
Hypoalbuminaemia	1 (0.8)
Vascular disorders	2 (1.7)
Hypertension	1 (0.8)
Hypertensive urgency	1 (0.8)
Gastrointestinal disorders	1 (0.8)
Vomiting	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.8)
Respiratory failure	1 (0.8)

Abbreviations: AE = adverse event; n = number of evaluable participants; N = number of participants; TEAE = treatment-emergent adverse event. a TEAEs were defined as any new AEs that began, or any pre-existing condition that worsened in severity, after the first ever dose of study medication in either VALIANT or VALE and up to 56 days beyond the last dose of study drug. b If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Note: AEs were coded to system organ class and preferred term using MedDRA Version 26.0.

TEAEs that led to treatment discontinuation included one (1.9%) participant who had a TEAE (end stage renal disease) that lead to treatment discontinuation in this study. In the combined studies, 5 (4.2%) participants experienced TEAEs that led to treatment discontinuation. These included 1 event of each of the following: nephrotic

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syndrome, infusion site reaction, herpes zoster meningoencephalitis, respiratory failure, and end stage renal disease.

No participants had a TEAE that led to dose interruption during this study. In the combined studies, 17 (14.2%) participants experienced TEAEs that led to dose interruption. The most frequently reported reasons for dose interruption were upper respiratory tract infection and COVID-19, each occurring in 3 (2.5%) participants.

No participants had a TEAE that led to study discontinuation during this study. In the combined studies, 2 (1.7%) participants experienced a TEAE (herpes zoster meningoencephalitis and respiratory failure) that led to study discontinuation.

2.12 Ongoing studies

VALE (NCT05809531), the long-term extension to VALIANT (NCT05067127 /APL2-C3G-310), is currently ongoing. The study is expected to complete in July 2027. No additional evidence is expected from this study in the next 12 months.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 VALIANT

VALIANT was a phase 3, prospective randomised, placebo-controlled, double-blinded, multicentre clinical study. The primary goal of this study was to assess the efficacy of twice-weekly SC doses of pegcetacoplan compared to placebo in patients with C3G or primary IC-MPGN based on a reduction in proteinuria after 26 weeks of treatment. The study enrolled a population that was generally representative of a real-world C3G or primary IC-MPGN population, including adults and adolescents with native kidneys or post-transplant recurrent disease. Patient demographics and disease characteristics at baseline were generally similar and balanced between the treatment groups.

2.13.1.1 Efficacy results: Proteinuria

VALIANT met the primary endpoint, demonstrating a statistically significant and clinically meaningful (68.1%) relative reduction in proteinuria at week 26 ($P < .0001$)

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in patients with C3G or primary IC-MPGN treated with pegcetacoplan compared to placebo (both in addition to background therapy). The primary endpoint result was consistent across all subgroups, including those based on disease type (C3G or primary IC-MPGN), age (adolescent or adult), and transplant status (native kidney or post-transplant kidney). 51% of patients achieved UPCR values below 1 g/g and a key secondary endpoint demonstrated a statistically significant 31x higher odds of achieving $\geq 50\%$ proteinuria reduction (60.3% in pegcetacoplan group vs 4.9% in placebo group; $p < 0.0001$). Furthermore, in a post-hoc analyses of the VALIANT study, 72% of patients with nephrotic range proteinuria (≥ 3 g/g) treated with pegcetacoplan achieved a clinically meaningful reduction in proteinuria at week 26, with 33% of patients achieving proteinuria reduction to < 1 g/g (100). Importantly, achieving $\geq 50\%$ proteinuria reduction and reducing proteinuria to < 0.88 g/g, over short periods of 6-12 months, have been shown to significantly reduce the risk of kidney failure. (37, 41)

Proteinuria results at Week 52 were consistent with those at Week 26. The effect of pegcetacoplan on uPCR was sustained up to 52 weeks (67.2% reduction in the pegcetacoplan-to-pegcetacoplan group compared to baseline). Patients who switched from placebo to pegcetacoplan at the end of the RCP experienced a 51.3% reduction in uPCR by the end of the following 26-week OLP (Figure 6). Furthermore, when compared to baseline, 50.79% of the patients in the pegcetacoplan-to-pegcetacoplan group, and 40.98% in the placebo-to-pegcetacoplan group, had a $\geq 50\%$ reduction in uPCR at Week 52.

2.13.1.2 Efficacy Results: Kidney function/eGFR

At week 26, the composite renal endpoint ($\geq 50\%$ reduction in UPCR and $\leq 15\%$ reduction in eGFR) was achieved by significantly more patients in the pegcetacoplan (49.2% [31/63]) vs placebo (3.3% [2/61]) arm ($p < 0.0001$). Similar proportions of patients in the pegcetacoplan-to-pegcetacoplan group and placebo-to-pegcetacoplan group achieved this composite endpoint at week 52 in the OLP. Achieving a $\leq 15\%$ reduction in eGFR (or avoiding eGFR declines of $> 15\%$) is considered indicative of stable kidney function and has been validated as clinically meaningful – for example,

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RaDaR publications have demonstrated that eGFR declines of 15% are associated with a higher risk of kidney failure. (41)

Pegcetacoplan treatment resulted in a nominally significant and clinically meaningful reduction in the rate of decline of eGFR over 26 weeks compared to placebo (+6.3 mL/min/1.73 m² difference vs placebo (nominal p=0.03)). The rate of eGFR decline in these conditions has high variability, with an estimated interquartile range of –1.6 to –17 mL/min/1.73 m² per year (31). The eGFR decline observed over 26 weeks in the placebo group during the RCP in this study was in line with these results. Following the OLP, eGFR remained stable in the pegcetacoplan-to-pegcetacoplan group through 52 weeks. After initially declining in the placebo-to-pegcetacoplan group during the 26-week RCP, pegcetacoplan stabilised eGFR for the remainder of the overall 52-week treatment period.

eGFR is a key marker of kidney function and used to define kidney failure (115). In both C3G and primary IC-MPGN, progression to kidney failure is a significant sequela of the diseases. C3G leads to kidney failure in approximately 25% to 50% of patients, with a median time from diagnosis to eventual kidney failure between 4 and 8 years in adult patients (4, 27, 32, 33, 72, 116). For patients with primary IC-MPGN, approximately 40% to 60% will progress to kidney failure or death within 10 years (20, 73, 117-121).

2.13.1.3 Efficacy Results: Histopathology

The clinical benefits of proteinuria reduction and eGFR stabilisation as discussed above are further supported by the mechanistic evidence, specifically the observed reduction of glomerular C3c staining - a hallmark of the underlying pathophysiology of these conditions. Pegcetacoplan effectively cleared glomerular C3 deposition, providing compelling evidence that the significant proteinuria reduction and eGFR stabilisation were a consequence of ameliorating the pathophysiological drivers of disease in C3G and primary IC-MPGN. Pegcetacoplan treatment resulted in clinically significant clearance of glomerular C3 deposits at Week 26; glomerular C3 was reduced (≥ 2 OOM) in 74.3% (26/35) of pegcetacoplan-treated patients (nominal

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p<0.0001) and 71.4% (25/35) of treated patients had complete clearance of C3 deposits (no positive immunofluorescence) in the biopsy.

This reduction in glomerular C3c deposition may demonstrate that pegcetacoplan produces a disease-modifying effect by preventing the excessive generation of the complement components that accumulate in the kidney, driving inflammation and subsequent deterioration in kidney function.

Treatment with pegcetacoplan did not achieve a significant difference in the total activity score of C3G histologic index activity score compared to placebo. The C3G histologic index score (including total activity score and chronicity score) was developed in 2018 (4) as a prognostic tool to predict disease progression in patients with C3G. However, this endpoint has not been validated for longitudinal use to assess treatment effect and has notable limitations. Furthermore, there are limited current real world or clinical trial data regarding the natural evolution of the total activity score, largely due to the lack of serial kidney biopsies. Lomax-Browne et al. reported histology scores in 39 patients (31 with C3G and 8 with IC-MPGN) with a second biopsy of their native kidneys (33). Their analysis compared changes in the histology scores between the baseline and second biopsy, showing that activity score decreased over time regardless of treatment. More recently, other placebo-controlled clinical trials requesting repeated biopsies in their protocols failed to demonstrate a significant difference between the treatment and placebo groups in the total activity score in response to various treatments (109, 122).

2.13.1.4 Efficacy Results: Summary

Taken together, these positive effects of pegcetacoplan on proteinuria, kidney function (eGFR) and histopathology provide robust evidence for the efficacy of pegcetacoplan in C3G and primary IC-MPGN. Further analysis of the VALIANT 26-week RCP has demonstrated that results across this triad of efficacy outcomes have been consistent in key populations, including those with nephrotic range ($\geq 3\text{g/g}$) proteinuria at baseline and those on concomitant immunosuppression.

These efficacy outcomes of VALIANT align with the findings of the Kidney Health Initiative C3G Trial Endpoints Work Group Report, which concluded that showing a Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

favourable treatment effect on all three of these endpoints noted above could provide convincing evidence of efficacy. (34)

2.13.1.5 Safety Outcomes

Overall, pegcetacoplan was well tolerated in participants with C3G or primary IC-MPGN who remained on treatment with pegcetacoplan for 52 weeks or who switched from placebo after 26 weeks to pegcetacoplan for 26 weeks during the OLP. The incidence of serious or severe events was low- SAEs were reported in 11.7% of participants during the overall study. Most AEs were mild or moderate. TEAEs, SAEs, infusion-related TEAEs or infusion site reactions generally did not increase over time. No clinically meaningful safety trends or correlations were observed for serum chemistry, haematology and coagulation laboratory parameters or for vital signs or ECGs. Pegcetacoplan was well tolerated in key subgroups of age group (adolescents and adults) and transplant status (non-transplant or post-transplant). AEs leading the treatment discontinuation were infrequent and reported in 5% of participants during the overall study. No trends were observed leading to treatment or study discontinuation, and no rejection episodes or graft loss were reported in the post-transplant participants. During the RCP, no major differences were found for AESIs when comparing pegcetacoplan to placebo.

2.13.1.6 Conclusion

This study demonstrated that pegcetacoplan has a positive benefit-risk profile in the treatment of C3G and primary IC-MPGN. Statistically significant and clinically relevant proteinuria reduction, consistent across all patient subgroups, was shown in patients on pegcetacoplan. In addition, there were meaningful improvements on the endpoints of reduction in C3c staining on kidney biopsy and stabilisation of kidney function as measured by eGFR. Overall, the safety data collected to date indicate a favourable safety profile for pegcetacoplan in patients with C3G or primary IC-MPGN. No new safety signals for pegcetacoplan were identified.

Current standards of care for C3G and primary IC-MPGN, rare kidney diseases typically affecting adolescents and young adults, include nonspecific measures to manage proteinuria and provide symptom relief (9, 10). Existing treatment options do

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not prevent worsening kidney function or irreversible kidney damage associated with these conditions. Approximately 50% of patients progress to kidney failure within 10 years of diagnosis despite treatment (2, 6, 22, 72-76). Such patients will then require either dialysis or a kidney transplant, and disease recurrence occurs in most patients following transplant (77), (6, 22, 74, 76).

Another complement inhibitor, iptacopan, is undergoing a single technology appraisal, solely for the treatment of adult C3G patients. (71). Even its potential addition would still leave an unmet need for adolescent patients with C3G and all patients with primary IC-MPGN.

A therapy that targets complement hyperactivity, specifically C3 dysregulation present in all patients with C3G and primary IC-MPGN, could be a valuable addition to the treatment arsenal. Pegcetacoplan, a targeted C3 and C3b inhibitor, has demonstrated statistically and clinically significant reduction of proteinuria as well as positive effects on kidney function (eGFR) and histopathology in a well-designed phase 3 randomised study which included pre- and post-transplant C3G and primary IC-MPGN adults and adolescents. This provides compelling evidence for the effective treatment of a broad range of people with C3G and primary IC-MPGN.

2.13.2 VALE

This interim study analysis demonstrated that pegcetacoplan has a longer-term positive benefit-risk profile in the treatment of C3G and primary IC-MPGN. Pegcetacoplan treatment led to a sustained effect on substantial and clinical meaningful reduction in proteinuria and stabilisation of eGFR. These effects were sustained through to at least week 64.

The safety profile in the VALE study was consistent with the previously reported data from the VALIANT study, and, as of the data cutoff date for this report, no new safety signals for pegcetacoplan were identified with the additional follow-up period.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted in accordance with the NICE methods and the Centre for Reviews and Dissemination (CRD)(123) guidance to identify published economic models/ evaluations, cost and resource use data, as well as any relevant utility data for patients with C3G and IC-MPGN.

Searches were initially performed in September 2024 with a search cut-off date of 2014. Subsequent updates were conducted in August 2025. Due to the rarity of both conditions, the search had a global geographical scope to capture all relevant evidence. Full details of the SLR search strategy, study selection process, and results are presented in Appendix E.

The electronic searches found no economic models specifically developed for C3G or IC-MPGN. Due to the lack of disease-specific models, a targeted search was conducted to identify existing models that capture the general progression of CKD, of which five were identified. The results of the targeted search are presented in Table 60 below.

Among these, three models incorporate proteinuria within their structure: the FINE-CKD model, which evaluates long-term clinical and economic outcomes in patients with CKD and type 2 diabetes, focusing on cardiovascular and renal complications (124); the Chronic Kidney Disease Model, a flexible, general-purpose simulation model of CKD progression and treatment outcomes(125); and a U.S.-based Markov model comparing paricalcitol with calcitriol for the treatment of secondary hyperparathyroidism in CKD patients(126). Additionally, two models include albuminuria as a key parameter: a cost-effectiveness analysis of add-on empagliflozin versus standard care in managing CKD in Malaysia, Thailand, and Vietnam, based on an EMPA-KIDNEY-eligible population(127); and a model assessing the economic value of combining urine albumin-to-creatinine ratio (ACR) testing with estimated glomerular filtration rate (eGFR) screening in early CKD detection among patients with type 2 diabetes(128).

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Table 60: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Pochopien et al.(124)	2021	Cohort state-transition (Markov) model, 15 health states, Country perspective not specified, describes structure and validation only.	T2D + CKD (NR)	NR	NR	NR
Orlando et al.(125)	2011	Individual-level Monte Carlo Markov model, ~12 health states, US healthcare setting, describes structure and methods only.	US CKD population (NR)	NR	NR	NR
Nuijten et al.(126)	2009	Markov cost-utility model, 8 health states, US payer and societal perspectives.	CKD stages 1-5 (NR)	4.59 vs 4.17		Dominant
Varghese et al.(127)	2024	Individual patient simulation model, ~8 health states, Malaysia, Thailand, and Vietnam healthcare payer perspectives	CKD, EMPA-KIDNEY ITT (NR)	Malaysia: 6.15 vs 5.11, Thailand: 6.20 vs 5.13, Vietnam: 6.19 vs 5.13	Malaysia (MYR): 103,095 vs 107,144; Thailand (THB): 1,022,706 vs 1,041,037; Vietnam (VND): 850,572,228 vs 768,390,471	Malaysia/Thailand: Dominant; Vietnam: 77,838,407 VND/QALY

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Rossing et al.(128)	2023	Dynamic microsimulation/ Markov-style progression model, 8-10 health states, UK healthcare perspective, describes structure and methods only.	Adults with CKD (Mean 60 yrs)	NR	NR	NR

Abbreviations: CKD, chronic kidney disease; EMPA-KIDNEY, Study of Heart and Kidney Protection with Empagliflozin; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; MYR, Malaysian ringgit; NR, not reported; QALY, quality-adjusted life year; THB, Thai baht; T2D, type 2 diabetes; UK, United Kingdom; US, United States; VND, Vietnamese dong.

3.2 Economic analysis

The economic models identified in the SLR offered valuable structural and clinical insights to support the development of an economic model for pegcetacoplan, particularly in the context of simulating CKD progression and guiding the use of health states defined by both eGFR and UPCR, with disease progression modelled through transitions driven by eGFR decline.

3.2.1 Patient population

The patient population included in the economic evaluation consisted of adolescents (aged 12-17 years) weighing at least 42 kg and adult patients with primary C3G or IC-MPGN. This population aligns with the proposed MHRA label population, the VALIANT trial study population, and the final NICE scope of this appraisal.

The baseline cohort age, proteinuria level, and CKD stage from VALIANT are used as inputs in the model to account for variations in cost and health outcomes due to demographic factors. The baseline characteristics applied in the model are based on the VALIANT trial population and are summarised in Table 61.

Table 61: Baseline characteristics applied in the model

Parameter		Value	Use in the model
Age (mean)		25.97 years	Mortality risk, general population age/sex disutility
Weight (mean)		63.09 kg	SoC basket costs
Percentage male		43.55%	Mortality risk, general population age/sex disutility
	CKD 1	45.97%	Starting health state distributions

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Baseline distribution of CKD stages	CKD 2	20.97%	
	CKD 3	29.84%	
	CKD 4	3.23%	
	CKD 5	0.00%	
Baseline distribution of uPCR levels	<1g/g	8.87%	
	1-3 g/g	58.87%	
	>3g/g	32.26%	

Abbreviations: CKD, chronic kidney disease; SoC, standard of care; uPCR, urine protein to creatinine ratio.

3.2.2 Model structure

A de novo cost-effectiveness model was developed in Microsoft Excel, with the support of Visual Basic for Applications (VBA), to calculate the cost-effectiveness of pegcetacoplan compared with a basket of standard of care treatments for treating adult and adolescent patients with primary C3G and IC-MPGN. The evaluation was conducted from an NHS and personal social services (PSS) perspective.

This cost-effectiveness model was based on a cohort-level Markov model, with health states defined by eGFR and uPCR level. This model structure was deemed most appropriate as it builds upon the well-established and clinically defined states of CKD by adding uPCR-specific sub-groups. The use of uPCR-specific health states within CKD stages reflects findings from numerous previously published studies (12, 34, 129-133) identifying proteinuria as one of the most robust and modifiable predictors of long-term renal outcomes in patients with CKD. For full details of the supporting evidence detailed in the identified studies, see section 2.3.1. This approach is also aligned with a model structure previously submitted to NICE for sparsentan for treating primary IgA nephropathy (IgAN; TA1074)(134), another rare glomerular disease. Key features of the economic analysis are described in Table 62.

Table 62: Key features of the economic analysis

	Current evaluation	
Factor	Chosen values	Justification
Time horizon	Lifetime (maximum age of 100 years)	C3G and IC-MPGN are lifelong glomerular diseases; therefore, a lifetime time horizon was used in the base-case analysis to capture the full benefits of treatment over a patient's lifetime.

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Cycle length	3 months	Appropriate to capture relevant health events and transitions between health states. A shorter cycle length was not deemed suitable due to natural fluctuations, particularly in eGFR measurements, which could make it difficult to reliably track disease progression
Half-cycle correction?	Yes	Consistent with the NICE reference case.
Discount of 3.5% for utilities and costs?	Yes	Consistent with the NICE reference case.
Source of efficacy	Efficacy data used to derive transition probabilities between uPCR health states, progression to advanced CKD stages, and rates of eGFR decline by uPCR level were sourced from a post hoc analysis of the VALIANT trial data.	The VALIANT trial is a high-quality RCT directly comparing the intervention and key comparator of interest. Its use is therefore consistent with the NICE reference case.
Source of safety	Safety data used to identify adverse events for use in the model were sourced from VALIANT trial data.	Consistent with the NICE reference case.
Source of CV events	The probability of CV health events included in the model: • Imoisili 2024(135) • Bragazzi 2021(136) • Life Tables for the United States Social Security Area 1900-2100(137) • Scarborough 2022(138) The increase in risk of CV events according to CKD stage was sourced from Matsushita 2015(139).	The inclusion of CV events aids in capturing the full disease burden associated with C3G and IC-MPGN and ensures cost and quality of life aspects associated with these diseases are captured in the model. This enables an understanding of the full clinical and economic impact of pegcetacoplan on patients with C3G and IC-MPGN.
Source of utilities	Primarily sourced using data from VALIANT and supplemented using data from Sidhu et al. 2024(28). An additional disutility was applied in the model for patients with elevated uPCR levels using data from the VALIANT trial. The model assumes that any disutility from AEs experienced during the trial is captured within this data.	Utilities sourced from VALIANT and Sidhu et al. 2024(140) for different CKD stages provide utility values elicited from C3G and IC-MPGN patients. The use of VALIANT uPCR data allows the model to capture disutility resulting from elevated uPCR levels.
Source of costs	CKD and uPCR health state costs were estimated using a micro-costing approach. Expert clinical input was sought to establish expected healthcare resource use (HCRU) in different model health states. These HCRU estimates were subsequently applied to unit costs sourced from PSSRU and NHS National Cost Collection.	The methods applied align with committee-approved approaches used in prior NICE appraisals in similar indications (TA1074; IgAN)(134) and (TA937; IgAN)(141) to capture acute and ongoing costs associated with general disease management, dialysis and transplantations. These methods were deemed appropriate given the lack of HCRU

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	Costs for dialysis and transplant health states were estimated using NHS cost collection estimates.	information in the current C3G or primary IC-MPGN literature.
Treatment waning effect?	No waning effect	Advice from clinicians during the interviews detailed in section .11 indicated no rationale for a reduction in efficacy over time, given the established mechanism of action of pegcetacoplan. This assumption also aligns with the committees preferred assumption following the initial committee meeting for iptacopan for the treatment of adults with C3G.(142)

Abbreviations: AEs, adverse events; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; CV, cardiovascular; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IgAN, IgA nephropathy; SoC, standard of care; uPCR, urine protein to creatinine ratio.

Model health states

The model uses 23 health states consisting of three uPCR categories and one stable disease category. Each category is stratified across five CKD stages with an additional four health states for haemodialysis (HD), peritoneal dialysis (PD), transplant, and death. This structure is replicated for patients who have undergone a transplant in order to differentiate the costs and utilities for these patients. Therefore, the model consists of 45 health states in total.

Based on findings identifying uPCR as a key predictor of disease progression (see Section .3.1), uPCR ranges were used as the primary basis for defining health states in the cost-effectiveness model. To reflect CKD severity and progression more accurately, eGFR levels were incorporated as a secondary defining variable, informed by existing CKD model structures (see Section .1) and feedback received during an advisory board held by Sobi (Section .11).

Movement through the model

At the start of the model, patients are assigned to uPCR health states and CKD stages based on baseline VALIANT trial data.

At each cycle, patients transition between uPCR health states and CKD stages according to probabilities derived from the VALIANT trial data. Specifically, the rate of eGFR decline, and thus progression through CKD stages, is dictated by uPCR

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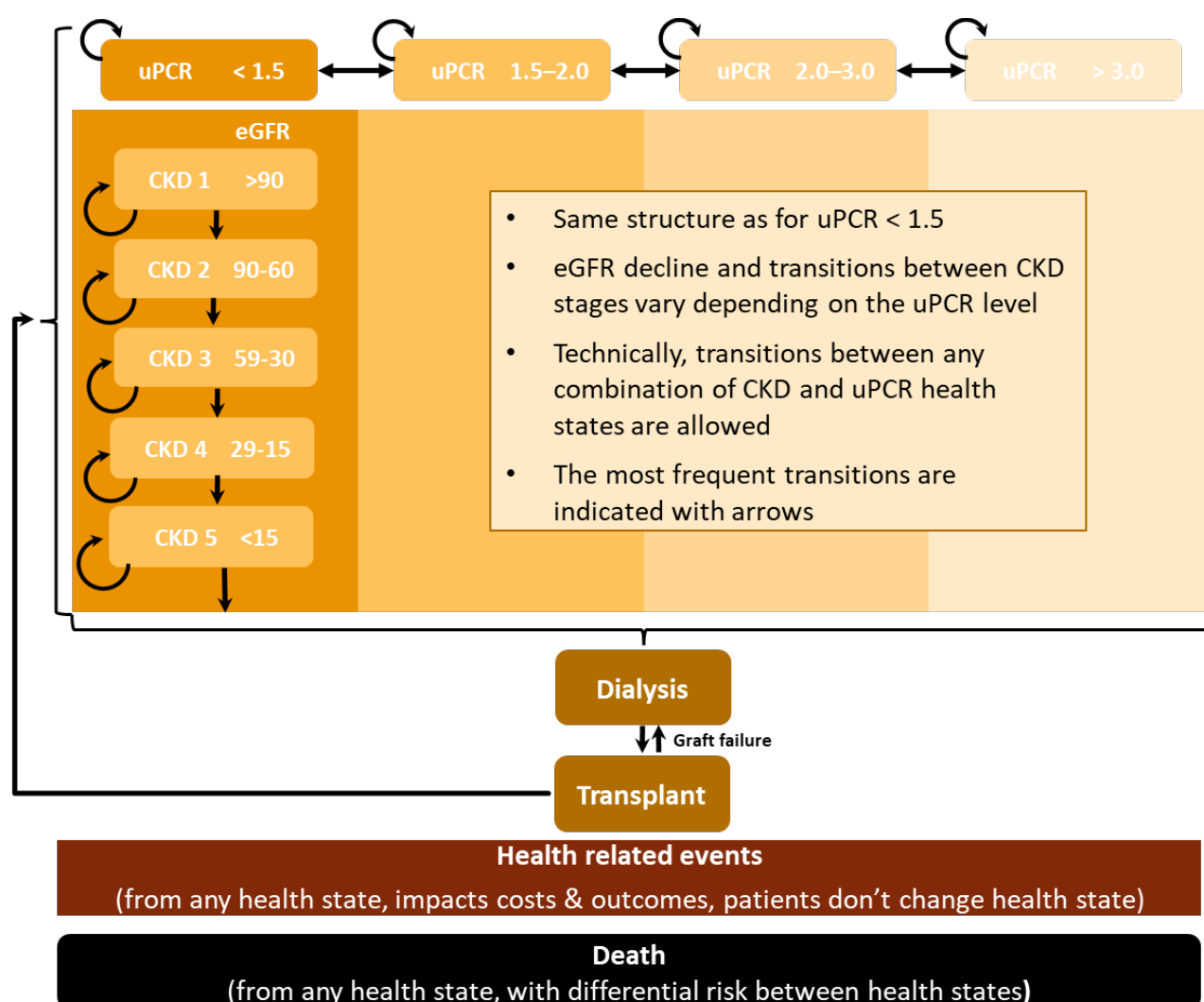
levels, with higher uPCR levels associated with more rapid kidney function deterioration (i.e. faster rate of eGFR decline).

Patients with uPCR <1 g/g may achieve disease stabilisation within the model. Stable disease is modelled as a distinct set of health states stratified by CKD stage, where uPCR is assumed to remain unchanged. It is further assumed that patients discontinue treatment while in stable disease and resume therapy upon disease relapse to maintain low uPCR levels. This assumption is based on advisory board feedback indicating patients achieving a UPCR of <1 g/g could discontinue treatment based on efficacy, with some reaching a non-progressive state (i.e. in complete remission). However, a biopsy may be required first, and some experts highlighted a lack of data to define the exact thresholds for stopping treatment, particularly as pegcetacoplan is a first-in-class disease-modifying therapy (Section .11). Nevertheless, the majority view expressed during subsequent interviews with clinical experts was that it would be reasonable to stop treatment in responders, aligning with the clinical approach in other rare glomerulonephritis conditions, with the option to restart in the event of a relapse (Section .11).

As the disease progresses, continued eGFR decline can result in ESKD, necessitating dialysis (subdivided into peritoneal dialysis or haemodialysis) or kidney transplantation, treated as separate health states within the model. After transplantation, patients transition to new post-transplant health states, with additional associated costs, based on their uPCR levels and CKD stage. Although eGFR typically improves in the short-term following transplant, it declines again over time, depending on uPCR levels. This deterioration may lead to the need for further dialysis or subsequent transplants.

A schematic of the model structure is presented in Figure 19.

Figure 19: Model schematic



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

Pegcetacoplan treatment effect modelling

Results from the VALIANT trial (Section) demonstrated that pegcetacoplan treatment impacts disease progression by reducing C3c staining on kidney biopsy, indicating suppression of complement-mediated injury at the tissue level. This upstream effect translates into reductions in uPCR levels, thereby slowing the decline in eGFR and delaying progression through the CKD stages. Furthermore, patients receiving pegcetacoplan may have a higher probability of disease stabilisation compared to those on standard care, due to achieving lower uPCR levels, with a greater proportion of patients expected to reach uPCR levels <1 g/g.

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Consequently, these patients spend less time in advanced CKD stages and on dialysis, resulting in both cost savings and improved quality of life.

An additional long-term benefit of pegcetacoplan is the decreased need for kidney transplants. The model captures this impact through both direct cost savings and utility gains, as patients avoid undergoing expensive surgical procedures. Moreover, by applying the concept of opportunity cost, the model accounts for kidneys no longer required by the treated population, which can be reallocated to other patients on the NHS transplant waiting list. This redistribution generates further cost savings and QALY gains for the wider NHS population, highlighting the wider value of the treatment to the healthcare system.

3.2.3 Intervention technology and comparators

Pegcetacoplan

Pegcetacoplan is a targeted C3 therapy developed to control the overactivation of the complement cascade, a component of the immune system that, when dysregulated, can contribute to the development and progression of various serious diseases. Pegcetacoplan is already approved for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) under the brand name Aspaveli®.

Pegcetacoplan can be given by a healthcare professional or administered by the patient or caregiver following proper instructions. Pegcetacoplan is administered twice weekly as a 1,080 mg subcutaneous infusion with a commercially available syringe system infusion pump that can deliver doses up to 20 mL. The twice-weekly dose should be administered on Day 1 and Day 4 of each treatment week. Treatment is intended to be an add-on to existing SoC and lifelong unless its discontinuation is clinically indicated.

Standard of care

There are well-defined clinical guidelines provided by KDIGO for the treatment and management of glomerular disease, including C3G and primary IC-MPGN(9). KDIGO recommends initial treatment with renin-angiotensin system inhibitors, specifically angiotensin-converting enzyme inhibitors (ACEis) and/or angiotensin

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receptor blockers (ARBs), titrated to the maximum tolerated dose to reduce proteinuria and control blood pressure. For patients with moderate to severe disease and no evidence of monoclonal gammopathy, immunosuppressive therapy with mycophenolate mofetil in combination with systemic corticosteroids is advised, with consideration of complement inhibitors (e.g., eculizumab) if initial therapy fails. Lifestyle modification and dietary sodium restriction are also emphasised as part of disease management to help achieve proteinuria reduction targets.

Although not yet formally endorsed by KDIGO for use in C3G or IC-MPGN due to a lack of indication-specific evidence at the time of guidance, sodium-glucose cotransporter 2 inhibitors (SGLT2is) have recently been shown to slow the progression of renal disease in nondiabetic proteinuric nephropathies(143). Their antiproteinuric and renoprotective effects are widely recognised, and off-label use in glomerular diseases, including C3G, is increasingly being adopted in clinical practice for the treatment of adult patients(144).

This standard of care is considered comparable to the placebo arm in the VALIANT trial, which serves as the primary comparator in the cost-effectiveness analysis. The included therapies and the percentage of patients who use each included therapy (Table 63) in the analysis reflect the concomitant medications recorded in the safety analysis set during the randomised period of the VALIANT trial.

Table 63: Percentage of usage of SOC treatment

SOC treatments	Proportion of patients receiving each SOC treatment in the model
ACEi/ARB	██████████
Immunosuppressants	██████████
Systemic corticosteroids	██████████
SGLT2i	██████████

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB; angiotensin receptor blockers; SGLT2i; sodium-glucose cotransporter-2 inhibitor; SoC, standard of care

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There are currently no licensed therapies for IC-MPGN that slow, halt, or reverse disease progression, resulting in limited treatment options for these patients in particular.

Eculizumab is currently available for the treatment of recurrence of C3G post-kidney transplant(145). However, due to limited evidence regarding its widespread use in clinical practice in the UK and the lack of robust data confirming its efficacy in stabilising eGFR and reducing uPCR in patients with C3G, eculizumab was not included in the base case analysis. This assumption is likely conservative, given the additional costs of eculizumab and the limited clinical evidence supporting improved outcomes. As a result, the model would be expected to show higher costs in the SOC arm without a meaningful impact on health outcomes.

Iptacopan

Iptacopan is a selective factor B inhibitor licensed for the treatment of C3G and is currently going through the NICE appraisal process as a treatment for adults with C3G. Although iptacopan is not currently recommended by NICE at the time of submission, it is expected to potentially become part of the NHS treatment pathway for C3G patients in the near future. As such, the company has included an analysis comparing its treatment to iptacopan for the committee's consideration.

The efficacy of pegcetacoplan was compared to iptacopan within an indirect treatment comparison. This analysis was based on two pivotal phase 3 trials, VALIANT(146) and APPEAR-C3G(147), which evaluated pegcetacoplan and iptacopan, respectively (Section).

3.3 Clinical parameters and variables

3.3.1 Key trial endpoints for modelling

Relationship between eGFR and uPCR

A large body of evidence highlights the prognostic significance of proteinuria across chronic kidney diseases, particularly in glomerular diseases such as C3G and IC-MPGN(129-132), and establishes it as both a marker of disease severity and a

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modifiable target for improving long-term renal outcomes(41), with regulators recognising proteinuria as a primary endpoint in the pivotal studies of pegcetacoplan and iptacopan(146, 147).

The Modification of Diet in Renal Disease (MDRD) Study was a pivotal investigation into the impact of blood pressure and proteinuria on CKD progression. It showed that elevated proteinuria levels, particularly above 1 g/day, were strongly associated with faster declines in eGFR(129).

Expanding on this evidence, Marques 2022(130) assessed the prognostic importance of early proteinuria reduction in patients with primary glomerular diseases. In a cohort of 197 patients followed for a median of 6.5 years, achieving proteinuria <1 g/day within the first year was associated with a 55% reduction in the risk of significant eGFR decline, independent of baseline kidney function or proteinuria.

The BRIGHTEN study, evaluated in a post hoc analysis by Gohda 2023(131), further reinforced this pattern. It showed that patients with uPCR ≥ 3.5 g/g had the highest risk of rapid kidney function decline, defined as an annual eGFR loss >5 mL/min/1.73 m².

In a separate multicentre cohort study, Troost 2021(132) explored the relationship between proteinuria and outcomes in patients with focal segmental glomerulosclerosis (FSGS). The study found that reductions in proteinuria, even if partial, were associated with significantly improved kidney survival, delayed onset of ESKD, and reduced need for dialysis. These findings affirm the utility of proteinuria as a therapeutic endpoint in both clinical trials and practice.

A series of recent studies has focused specifically on rare glomerular diseases, including C3G and IC-MPGN (see section 1.3.3). Masoud 2024(12) used longitudinal data from the UK RaDaR registry to analyse outcomes in patients with biopsy-confirmed C3G or IC-MPGN. While proteinuria at diagnosis did not independently predict kidney failure, early reductions in proteinuria were highly prognostic. A $\geq 50\%$ decrease in UPCR within 12 months was associated with a 67% lower risk of kidney

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failure (HR 0.33, 95% CI 0.17–0.63), while achieving a UPCR <0.88 g/g at 12 months was associated with an 87% lower risk (HR 0.13, 95% CI 0.03–0.56). These results, as well as the reference to these outcomes in terms of clinical treatment goals (section 1.3.4) highlight the prognostic significance of short-term proteinuria trends over static baseline values.

Complementary findings were reported by Caravaca-Fontán 2025(133) in a multicentre Spanish cohort. The authors observed that time-dependent increases in proteinuria were associated with worse renal outcomes, while patients who achieved $\geq 50\%$ proteinuria reduction had substantially lower risk of kidney failure (HR 0.61; 95% CI 0.46–0.75, $p < 0.001$). Notably, early reductions of 30% at 6 months or 50% at 12 months were linked to slower eGFR decline. Patients maintaining time-averaged proteinuria <1 g/day experienced the most favourable outcomes.

Finally, in the context of regulatory science and drug development, Nester 2024(34) reported on the Kidney Health Initiative's working group for C3G trial endpoints. The panel concluded that meaningful reductions in proteinuria, especially when combined with stabilisation or improvement in eGFR, are valid indicators of treatment efficacy.

Early and sustained reductions in proteinuria are associated with slower eGFR decline, reduced risk of kidney failure, and improved survival. In the context of diseases such as C3G and IC-MPGN, evidence supports incorporating proteinuria reduction into risk stratification models and the evaluation of treatment response. This modelling approach is also consistent with three models in CKD identified in the SLR (see Section .1).

3.3.2 Transition probability calculations

As the model is a state-transition Markov model, transition probability matrices were developed to define the movement of a cohort of patients between the modelled health states.

Treatment effect modelling

When modelling transition probabilities between health states, defined primarily by uPCR, a single transition matrix approach was used in the base case, capturing the overall changes in uPCR across the entire VALIANT study period.

This method captures the full disease trajectory, incorporating both initial treatment effects and sustained changes in kidney function, and is well-suited to reflect the overlapping acute and chronic damage processes that are typical of progressive glomerular diseases.

This method of using the entire study period to generate the clinical parameters used in the model was extended to the calculation of average eGFR decline, by uPCR category.

The EMA (via the EPAR), in its assessment of the marketing authorisation application for sparsentan in IgA nephropathy, expressed a clear preference for the use of total slope over chronic slope when capturing treatment effects on eGFR. This preference was based on the rationale that total slope reflects kidney function over the entire study period, minimises bias from post-randomisation events, and reduces the risk of false-positive findings, particularly when an acute decline in eGFR occurs upon treatment initiation.

This position was further reinforced by the FDA, which explicitly requested the use of total slope for final regulatory evaluation, underlining its importance for assessing disease-modifying effects.

While these regulatory precedents refer to eGFR, the underlying rationale is directly transferable to uPCR: using the total change from baseline of uPCR ensures that transient acute effects do not obscure the sustained therapeutic impact of treatment over time.

The use of total uPCR change from baseline is further supported by real-world observational evidence demonstrating that sustained reductions in proteinuria are predictive of improved long-term renal outcomes in patients with C3G and IC-MPGN.

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A recent analysis from the UK RaDaR registry, Masoud 2024(12), found that uPCR levels at 12 months were strongly associated with subsequent risk of kidney function decline and kidney failure. Specifically, maintaining a uPCR below 150 mg/mmol at 12 months was associated with a significantly lower risk of both $\geq 30\%$ eGFR decline and progression to kidney failure.

These findings underscore the importance of evaluating durable reductions in proteinuria over longer periods, as captured by a long-term changes from baseline approach, rather than focusing on early or short-term changes alone.

uPCR state transitions

Transition probabilities between uPCR levels were derived from a statistical analysis of patient-level data from the VALIANT trial using R software version 4.4.2.

Regression models were developed to estimate the probability of a patient being in a specific health state at a given visit, based on their health state at the previous visit, considering the cycle length (i.e. 12 weeks) and other covariates, including:

- Treatment variable (pegcetacoplan, no pegcetacoplan)
- Patients' age
- Patients' sex

Model types assessed:

- Ordered logistic regression
- Multinomial logit model

As patients in the placebo group in VALIANT were crossed over to pegcetacoplan treatment arm after 26 weeks, placebo data beyond this point were excluded from regression analyses. For the pegcetacoplan arm, the base case incorporated all 52 weeks of treatment arm data from VALIANT to maximise data utilisation. To test robustness of the data, a scenario analysis was performed using only randomised data from the first 26 weeks in both arms, thereby maintaining consistent time horizons across treatment groups.

AIC values for all models are presented in Table 64. A summary of each model, including the number of patients used to inform each transition, can be found in the accompanying statistical analysis plan report (Appendix M).

Table 64: AIC values for the transition probability models

Model	AIC
Multinomial (AGE, SEX, ARM, HS)	520.24
Multinomial (AGE, ARM, HS)	517.23
Multinomial (SEX, ARM, HS)	516.29
Multinomial (ARM, HS)	513.30
Ordered logistic (AGE, SEX, ARM, HS)	515.98
Ordered logistic (AGE, ARM, HS)	516.10
Ordered logistic (SEX, ARM, HS)	516.67
Ordered logistic (ARM, HS)	516.72

Abbreviations: AIC, Akaike information criterion; HS, health state

Multinomial logistic regression using only the variable for treatment arm and health state during the previous visit was considered the most fitting based on AIC, most parsimonious based on having the fewest covariates, and most flexible given that multinomial models are able to capture non-linear transitions better. Parameters of the chosen regression model are presented in Table 65.

Table 65: Regression parameters of the chosen transition probability model

Variable	To uPCR 1.0-3.0	To uPCR >3.0
Intercept	██████	██████
From uPCR 1.0-3.0	██████	██████
From uPCR >3.0	██████	██████
Placebo arm	██████	██████

The transition matrices resulting from this regression model for the standard of care and pegcetacoplan are presented in Table 66 and Table 67, respectively.

Table 66: uPCR transitions SoC

From\To	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	██████	██████	██████

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uPCR 1.0 - 3.0 g/g			
uPCR >3 g/g			

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

Table 67: uPCR transitions with pegcetacoplan

From\To	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g			
uPCR 1.0 - 3.0 g/g			
uPCR >3 g/g			

Abbreviations: uPCR, urine protein to creatinine ratio

Due to the lack of access to patient-level data from the iptacopan trial, it was not possible to estimate key model parameters for iptacopan—such as transition probabilities, eGFR decline, and the probability of disease stabilisation—in the same way as for pegcetacoplan. As a result, treatment differentiation was based on uPCR outcomes derived from outcomes from the indirect treatment comparison (Section). Specifically, an odds ratio (OR) of (Table 68) was applied to reflect the probability of achieving uPCR <1 g/g with iptacopan.

Table 68. Results of Bucher’s indirect comparison between pegcetacoplan and iptacopan for proteinuria-related (24h vs 24h) outcomes.

Outcome	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
UPCR thresholds (24h vs 24h), odds ratio [95% CI]			
≥3 (g/g)			
1-3 (g/g)			
<1 (g/g)			
≥50% reduction			

Abbreviations: UPCR, urine protein-creatinine ratio

The probability of transitioning to the uPCR <1.0 state was modified using this odds ratio to reflect iptacopan’s relative efficacy. The probabilities of transitioning to the uPCR 1.0–3.0 and >3.0 states were then calculated as the complement of the probability of achieving uPCR <1.0, proportionally allocated using pegcetacoplan’s

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original transition weights to these states. A summary of the iptacopan UPCR transition probabilities used in the model are shown in Table 69.

Table 69. uPCR transitions with iptacopan

From\To	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	██████	██████	██████
uPCR 1.0 - 3.0 g/g	██████	██████	██████
uPCR >3 g/g	██████	██████	██████

Abbreviations: UPCR, urine protein-creatinine ratio

CKD stage transitions

The initial literature review suggested that eGFR decline accelerates with increasing uPCR levels. To validate this relationship, an analysis of patient-level data from the VALIANT trial was conducted using R software version 4.4.2. Similar to uPCR transition probability calculations, 26-week placebo data and 52-week pegcetacoplan data from VALIANT were used in the model base case, with scenario analysis explored to assess the impact of using 26-week data from both trial arms.

A linear regression model was used to assess the relationship between changes in eGFR and uPCR, which was categorised into three distinct subgroups based on uPCR values and treatment used. Patient age and sex were assessed as variables but not included in the final model as they were not found to be statistically significant. Model outcomes received from the regression are presented in Table 70.

Table 70: eGFR decline linear regression analysis results

Variable	Estimate	P-value
Intercept	██████	0.430
Placebo arm	██████	0.143
uPCR 1.0 - 3.0 g/g	██████	0.336
uPCR >3 g/g	██████	0.109

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

The eGFR decline inputs resulting from the regression are presented in Table 71.

Patients with uPCR < 1.0 treated with pegcetacoplan showed an increase in eGFR, indicating stabilisation of kidney function. However, extrapolating this eGFR

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improvement over the model time horizon was considered inappropriate and lacking clinical face validity. Therefore, a conservative assumption was made: no change in eGFR was applied for patients with uPCR < 1.0 while on pegcetacoplan treatment.

The rate of eGFR decline for iptacopan was assumed to be the same as for pegcetacoplan, conditional on the corresponding uPCR level.

Table 71: eGFR decline depending on uPCR level

Treatment/ uPCR level	Pegcetacoplan/iptacopan	Standard of care
uPCR <1.0	■	■
uPCR 1.0 - 3.0	■	■
uPCR >3	■	■

Abbreviations: eGFR, estimated glomerular filtration rate; uPCR, urine protein to creatinine ratio. Notes: * Conservatively, no change in eGFR was assumed; the regression result indicated an increase in eGFR of 0.87

The eGFR decline estimates described above served as the basis for deriving transition probabilities between CKD stages in the model (Table 73). These probabilities were calculated by considering the baseline distribution of patients across CKD stages (Table 61), the eGFR ranges defining each stage (10) (Table 72), and the corresponding rates of eGFR decline.

Table 72: CKD stages and corresponding eGFR

CKD state	Corresponding eGFR (mL/min/1.73 m ²)
CKD 1	eGFR > 90
CKD 2	eGFR 60-90
CKD 3	eGFR 59-30
CKD 4	eGFR 15-29
CKD 5 (ESRD)	eGFR <15

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (measured as 35mL/min/1.73 m²); ESRD, end-stage renal disease

Table 73: Probability of transition to the proceeding CKD stage according to eGFR

CKD stage	uPCR group	Probability of change of CKD per model cycle			
		Pegcetacoplan/iptacopan		SOC	
CKD 1	Stable disease				
	uPCR <1.0				
	uPCR 1.0 - 3.0				
	uPCR >3				
CKD 2	Stable disease				
	uPCR <1.0				
	uPCR 1.0 - 3.0				
	uPCR >3				
CKD 3	Stable disease				
	uPCR <1.0				
	uPCR 1.0 - 3.0				
	uPCR >3				
CKD 4	Stable disease				
	uPCR <1.0				
	uPCR 1.0 - 3.0				
	uPCR >3				
CKD 5	Stable disease				
	uPCR <1.0				
	uPCR 1.0 - 3.0				
	uPCR >3				

Transitions to dialysis

The model assumes that patients who reach CKD stage 5 require dialysis. Specifically, the model assumes that 100% of patients transition to dialysis after remaining in CKD stage 5 for one cycle, regardless of treatment received.

Two types of dialysis were included in the model: haemodialysis (HD) and peritoneal dialysis (PD). Based on data provided by United Kingdom Renal Registry (UKRR) 27th annual report (148), the population requiring dialysis was split 88.00% undergoing HD and 12.00% undergoing PD.

Transitions to transplants

In the model, patients may undergo kidney transplantation from the dialysis or CKD5 health state, based on a per-cycle probability. This probability was derived from UK data obtained from the RaDaR registry. According to these data, the median time from starting dialysis to receiving a transplant was 14.4 months. This median time

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was then converted into a per-cycle transition probability for use in the model. The same probability was assumed for both first and subsequent transplants (Table 74).

Table 74: Probability of kidney transplantation from dialysis

Median number of months from dialysis initiation to transplant	Calculated probability of transplant per model cycle (3-months)
14.4	13.45%

Based on estimates from Pruett 2021(149), a 95.32% probability of graft survival was assumed and applied in the first cycle following transplantation.

The Pruett 2021 study also provided estimates for the post-transplant distribution of patients across CKD stages (Table 75). The model assumes that patients will return to the baseline distribution of uPCR levels sourced from VALIANT following a transplant (Table 61).

Table 75: Post-transplant distribution of patients across CKD stages

Parameter		Value
Distribution of CKD stages post-transplant	CKD1	6.57%
	CKD2	32.95%
	CKD3	52.24%
	CKD4	8.23%
	CKD5	0.00%

Abbreviations: CKD, chronic kidney disease

An alternative source from Masoud et al. 2025 was explored for first and subsequent kidney grafts survival in scenario analysis based on clinical feedback that second or subsequent transplants could deteriorate at a faster rate than initial transplants.

According to Adelphi DSP data, among patients in the EU-5 requiring transplantation, 16.8% were considered unsuitable for transplantation by their treating nephrologist. This figure was applied in the model to patients who would have transitioned to receive a transplant, but instead remain on dialysis.(150)

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3.3.3 Stable disease

Stable disease in the literature

Caravaca-Fontán et al. 2020(151) investigated the clinical effectiveness of mycophenolate mofetil (MMF) in combination with corticosteroids in patients with C3G. The multicentre retrospective cohort study was conducted under the coordination of the Spanish Group for the Study of Glomerular Diseases (GLOSEN) and included 97 patients diagnosed with C3G across 39 nephrology centres in Spain.

Given the heterogeneous nature of C3G and the lack of standardised treatment protocols, the study aimed to evaluate therapeutic outcomes while also introducing and systematically analysing the concept of remission in this context. Remission was defined using two clinical endpoints: 'complete remission' (CR), characterised by normalisation of both eGFR and proteinuria, and 'partial remission' (PR), defined as a significant reduction in proteinuria accompanied by stabilisation or improvement in eGFR without full normalisation. These categories were applied to assess treatment response among 97 patients, 47% of whom achieved remission, 19% complete, and 29% partial, after a median of 14 months. The study also evaluated the durability of remission and found that one-third of patients who initially responded relapsed after discontinuing MMF. This indicates that treatment is often discontinued in clinical practice once remission is achieved, although this approach may carry a risk of relapse.

Stable disease in the cost-effectiveness analysis

Following Caravaca-Fontán 2020(151), stable disease in the model was defined using the criteria for normalisation of both eGFR and proteinuria. According to results from VALIANT on eGFR decline (see section 2.6.1.2), patients who had a uPCR below 1.0 g/g maintained stable eGFR.

The model applies a more stringent definition of stable disease, defined as a UPCR of less than 0.5 g/g. This requirement was restricted to be broadly consistent with the definition of remission in clinical practice, as described by Caravaca-Fontán 2020(151).

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Applying this definition to the VALIANT trial data, we identified the number of patients who achieved stable disease at the end of follow-up, 26 weeks for the placebo group and 52 weeks for the pegcetacoplan group.

Due to the structure of the model calculations, the number of patients with stable disease was applied those who achieved uPCR < 1.0 g/g, and this was converted into a per-cycle probability. The results of this analysis are presented in Table 76.

Additionally, a further more stringent definition of stable disease (<0.3 g/g uPCR) was considered. However, trial results showed that no patients receiving standard of care achieved this UPCR level. Since this did not reflect clinical practice, the definition was not used in the model.

A similar approach to that used to estimate UPCR transition probabilities for iptacopan (Section 3.2; i.e. application of a  OR to pegcetacoplan probability, resulting in a lower probability of patients achieving disease stabilisation compared to patients on pegcetacoplan) was used to estimate the probability of achieving stable disease for patients receiving iptacopan.

Table 76: Probability of disease stabilisation

Parameter	Pegcetacoplan	Standard of care	Iptacopan
Follow-up	52 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			

Abbreviations: uPCR, urine protein to creatinine ratio.

The second model parameter defining disease stabilisation is its duration, indicating the per-cycle probability of relapse. In Caravaca-Fontán 2020(151), one-third of patients with C3G who achieved ‘complete remission’ on corticosteroids plus MMF experienced a relapse after treatment discontinuation. The median time to relapse was 26 months (IQR: 15–79 months), suggesting sustained remission in a significant

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proportion of patients. This duration of stable disease was applied the same across all treatments. For the purposes of the model calculations, the median time spent in the stable disease state was converted into a per-cycle probability of relapse. The duration of the stable disease and the probability of disease relapse included in the model are presented in Table 77.

Table 77: Duration of the stable disease and probability of disease relapse

Treatment	Median number of months of stable disease	Probability of relapse per cycle
Pegcetacoplan	26	7.69%
Iptacopan	26	7.69%
Standard of Care	26	7.69%

Patients in the stable disease health states are not assumed to observe declines in eGFR, or transition to a later CKD stage. This assumption was explored in scenario analysis using the alternative assumption that patients in stable disease would experience a decline of $-0.18 \text{ mL/min/1.73 m}^2$ per 3-month model cycle, accounting for age-related eGFR decline observed in the general population. The decline rate of -0.18 per cycle was derived from the midpoint of the annual range reported by Guppy et al. (2024)(152), who observed an annual eGFR decline of -0.37 to $-1.07 \text{ mL/min/1.73 m}^2$ per year in individuals without hypertension which was adjusted to the 3-month model cycle.

3.3.4 Cardiovascular events

Research from Matsushita 2015(153) has shown that large variation from normal eGFR level ($\sim 90 \text{ mL/min per } 1.73 \text{ m}^2$) increases the risk of cardiovascular (CV) events such as heart failure, stroke, coronary heart disease, and cardiovascular mortality. As a result, four CV events were included in the model: stroke, heart failure, CV mortality, and myocardial infarction. The sources for the general population risk of each included event are shown in Table 78.

Table 78: General population CV event sources

Event	Source

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Occurrence of stroke	Imoisili 2024(135)
Heart Failure	Bragazzi 2021(136)
CV mortality	Life Tables for the United States Social Security Area 1900-2100(137)
Occurrence of MI	Scarborough 2022(138)

Abbreviations: CV, cardiovascular; MI, myocardial infarction.

Since CV event rates were reported for different age groups across the studies, the definitions of incidence and prevalence were standardised into 5-yearly age groups. All values falling within specific age ranges were treated as being represented by the same value. Table 79 presents the probabilities of CV health events occurring within the model.

The stroke event was modelled cumulatively; after experiencing an initial stroke, patients were considered to be in a post-stroke health state, with associated costs and disutility applied. Post-stroke patients could experience a subsequent stroke with the same probability as a first stroke (i.e., no adjustment was made for recurrent stroke risk).

Table 79: Probabilities of health events per cycle

Age category	Stroke	Health Failure	CV mortality	Myocardial infarction
0-4	0.23%	0.10%	0.15%	0.00%
5-9	0.23%	0.10%	0.15%	0.00%
10-14	0.23%	0.10%	0.15%	0.00%
15-19	0.23%	0.11%	0.45%	0.00%
20-24	0.23%	0.13%	0.45%	0.00%
25-29	0.23%	0.20%	0.45%	0.00%
30-34	0.23%	0.30%	0.45%	0.00%
35-39	0.23%	0.35%	0.45%	0.00%
40-44	0.23%	0.50%	0.45%	0.00%
45-49	0.96%	0.98%	0.45%	0.00%
50-54	0.96%	1.47%	0.39%	0.00%
55-59	0.96%	1.75%	0.39%	0.00%
60-64	0.96%	2.77%	0.39%	0.01%
65-69	1.98%	4.43%	0.64%	0.01%
70-74	1.98%	4.95%	0.64%	0.02%
75-79	1.98%	5.18%	0.64%	0.03%
80-84	1.98%	4.35%	0.64%	0.05%
85-89	1.98%	3.01%	0.47%	0.09%

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90-95	1.98%	1.34%	0.47%	0.09%
95-99	1.98%	0.35%	0.47%	0.09%
100-104	1.98%	0.35%	0.47%	0.09%

Abbreviations: CV, cardiovascular.

For each type of CV event, data from Matsushita 2015(139) regarding the particular hazard ratio for each CKD stage was extracted and interpreted as an increase in CV risk for a particular health state. Table 80 presents the HR for each CV health event according to the associated CKD stage.

Table 80: Impact of CKD on the risk of health events

CKD stage	HR
Stroke	
CKD1	1.13
CKD2	1.00
CKD3	1.11
CKD4	1.52
CKD5	1.52
HD	1.52
PD	1.52
Health failure	
CKD1	1.09
CKD2	1.11
CKD3	1.71
CKD4	2.52
CKD5	2.52
HD	2.52
PD	2.52
CV mortality	
CKD1	1.32
CKD2	1.10
CKD3	1.58
CKD4	2.62
CKD5	2.62
HD	2.62
PD	2.62
Myocardial infarction	
CKD1	1.00
CKD2	1.00
CKD3	1.73
CKD4	2.23
CKD5	2.23

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HD	2.23
PD	2.23

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HD, haemodialysis; HR, hazard ratio; PD, peritoneal dialysis.

3.3.5 Mortality

The general population mortality rate used in the model was accessed from the Office for National Statistics 2021-2023 Life table(154). The provided life tables separated the mortality rate between males and females at different ages. The data was averaged, considering the proportion of males from the VALIANT trial (see section 3.1), and subsequently transformed into a rate per model cycle (3-month).

According to the identified literature Quist 2025(155), progression of kidney disease has a significant impact on patients' risk of mortality. The increases in risk of death considered in the model for different CKD stages were applied using hazard ratios to the general population mortality rates. The hazard ratios applied to each CKD stage are presented in Table 81.

Table 81: Impact of CKD on mortality

CKD stage	HR
CKD1	1.14
CKD2	1.14
CKD3	1.33
CKD4	6.42
CKD5	9.49
HD	10.04
PD	10.04

Abbreviations: CKD, chronic kidney disease; HD, haemodialysis; HR, hazard ratio; PD, peritoneal dialysis.

The current model for pegcetacoplan adopts a conservative assumption that the risk of death among individuals with kidney failure remains constant over time, despite evidence to suggest that there is an increased risk of death in the first 3-6 months following kidney failure (56, 156-158). This approach was chosen to maintain simplicity and transparency in the model, avoiding excessive complexity that could arise from introducing additional tunnel states.

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3.3.6 Treatment modelling

Treatment discontinuation

The model base case captures discontinuation of pegcetacoplan treatment. Pegcetacoplan may be discontinued in any cycle, while standard of care continues throughout treatment in both model arms.

According to the VALIANT trial results, six patients discontinued pegcetacoplan during the study: ■■■ in the randomised controlled period, ■■■ in the open-label period (i.e. those who initiated the trial on pegcetacoplan), and ■■■ in the open-label period who had switched to pegcetacoplan (i.e. those who initiated the trial on placebo). Based on these data, a ■■■% per-cycle discontinuation rate was assumed in the model. Due to the absence of real-world data, the model assumes the same ■■■% per-cycle discontinuation rate for iptacopan.

Patients who progress to CKD stage 5 or require dialysis are no longer assumed to benefit from uPCR reduction and therefore do not receive pegcetacoplan or iptacopan. Patients who achieve stable disease discontinue all treatment; neither pegcetacoplan nor standard care is administered for these patients. This approach is aligned with current clinical practice (151).

Subsequent treatment

Kidney transplantation is modelled as leading to initial improvements in both CKD stage and uPCR levels and may result in stable disease for some patients. For post-transplant patients who do not achieve stable disease, pegcetacoplan or iptacopan treatment is continued if they did not discontinue treatment before transplant. Based on the mode of action of pegcetacoplan, and feedback from clinical experts, the model assumes the same treatment efficacy of pegcetacoplan post-transplant as pre-transplant.

For those in the SOC and iptacopan arm, treatment with SOC and iptacopan is assumed to continue following a transplant, respectively.

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Treatment effect waning

Clinical data from the VALIANT trial and long-term evidence in paroxysmal nocturnal haemoglobinuria (PNH) show no indication of waning in pegcetacoplan's C3 inhibition. C3 inhibition is expected to interrupt the process in C3G/primary IC-MPGN that leads to both proteinuria and ESKD (see section 1.3]). Consequently, no decline in treatment efficacy is anticipated, and waning was not incorporated into the model.

3.3.7 Adverse events

Adverse events were not included in the cost-effectiveness analysis. Data from VALIANT's randomised control period highlights that only six treatment-emergent adverse events (TEAEs) in each trial arm were considered "serious" (i.e., resulted in death, life-threatening situation, hospitalisation, etc.) and therefore may have led to additional healthcare-related costs borne by the healthcare provider. Of these 12 serious TEAE, no single adverse event occurred in $\geq 5\%$ of the trial population. In light of this, the model does not include any adverse event-related costs or explicit utility adjustments.

3.4 Measurement and valuation of health effects

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

In the VALIANT study, EQ-5D-5L questionnaire responses were collected and used to derive health state utilities through regression analysis of patient-level data. The resulting utility values were mapped to EQ-5D-3L and were found to be generally consistent with those reported in previous studies in CKD populations (Cooper 2020(159)).

However, this comparison is limited to patients in earlier CKD stages due to the VALIANT trial including few patients in CKD stage 4, none in CKD stage 5, and non on dialysis, at baseline. Additionally, no cardiovascular events were recorded in the trial, making it not viable to estimate CV related disutilities directly.

However, the analysis did identify a relationship between uPCR levels and health state utilities, allowing for an estimation of additional disutility for patients with elevated uPCR levels.

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Utility mapping

The EQ-5D-5L utility values obtained from patient responses in the VALIANT study were first mapped to EQ-5D-3L in accordance with NICE guidance before being used in combination with Sidhu et al 2024 (140) to derive the utility values for health states in the model. EQ-5D-5L utility values were mapped to EQ-5D-3L values using the Decision Support Unit algorithm included in the “eq5d” R package.

3.4.2 Health-related quality-of-life studies

Relevant utility data for patients with C3G and IC-MPGN was captured as part of the SLR outlined in Section .1. Searches were initially performed in September 2024 with a search cut-off date of 2014. Subsequent updates were conducted in August 2025. The SLR was conducted in accordance with the NICE requirements and CRD guidance. Full details of the SLR search strategy, study selection process and results are presented in Appendix F.

Evidence identified in the SLR on the patient burden and impact on health-related quality of life (HRQoL), activities of daily living, and utilities for patients with C3G and primary IC-MPGN was scarce: only two articles reported on HRQoL using a generic patient-reported outcome instrument (Lafayette et al. 2024(68)) (Sidhu et al. 2024(160)) .

In the first study (Lafayette et al. 2024(68)) using Adelphi C3G DSP data, the EuroQol Visual Analogue Scale (EQ-VAS) instrument was used to assess HRQoL (Table 82). The study found that the 100 patients with C3G had a mean EQ-VAS score of 63.0. When evaluating mean EQ-VAS scores by chronic kidney disease (CKD) stages, patients who had CKD stages 1–3b reported scores that were comparable to one another (ranging from 63.6 to 66.7). Patients with CKD stages 4 and 5 had the lowest EQ-VAS score of 46.8.

The study also used the EQ-5D-5L questionnaire to assess the patient’s current health status and HRQoL (Table 82). Patients with C3G had a lower mean EQ-5D-5L score compared with the UK general population: 0.72 versus 0.89, respectively. Patients with CKD stage 1 had a mean EQ-5D-5L score of 0.67, while patients with stage 4 and 5 reported lower scores with a mean of 0.58.

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Table 82: Summary of mean EQ-VAS scores and EQ-5D-5L scores by CKD stage reported by Sidhu et al., (2024)

Patient population	Mean EQ-VAS score	Mean EQ-5D-5L score
Total (N = 100)	63.0	0.72
CKD stage 1 (n = 16)	63.6	0.67
CKD stage 2 (n = 35)	66.7	0.77
CKD stage 3a (n = 21)	66.3	0.80
CKD stage 3b (n = 13)	65.5	0.70
CKD stage 4 and 5 (n = 15)	46.8	0.58

Abbreviations: CKD stage 1: eGFR/GFR ≥ 90 mL/min/1.73 m²; CKD stage 2: eGFR/GFR 60–89.99 mL/min/1.73 m²; CKD stage 3a: eGFR/GFR 45–59.99 mL/min/1.73 m²; CKD stage 3b: eGFR/GFR 30–44.99 mL/min/1.73 m²; CKD stage 4: eGFR/GFR: 15–29.99 mL/min/1.73 m²; CKD stage 5: eGFR/GFR < 15 mL/min/1.73 m². CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-VAS, EuroQol Visual Analogue Scale

The second study (Sidhu et al. 2024(160)), which also used data from the Adelphi C3G DSP, demonstrated that among the 118 patients with C3G who completed the EQ-5D questionnaire, 74% reported experiencing anxiety and/or depression, while 65% noted feeling discomfort and/or experiencing pain. Additionally, 63% of respondents reported that they had difficulties performing their usual day-to-day activities, including in mobility, 42% experienced challenges with their physical mobility and self-care tasks, 30% struggled with tasks such as washing or dressing.

3.4.3 Adverse event disutilities

Health state utilities used in the analysis were derived from clinical trial data (see section 3.4.4), and it is therefore assumed that any disutility from AEs experienced during the trial was implicitly captured within this data.

3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

In the first instance, EQ-5D-5L data mapped to -3L from VALIANT were used in the model for CKD stages 1-2. Pooled VALIANT data were used for these patients as this represented the CKD stages of the majority of patients at baseline, and previous literature has indicated similarities in HRQoL outcomes amongst these two patient groups.

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Linear regression was used to estimate the impact of variables (baseline EQ-5D, age, uPCR level) on EQ-5D-3L values. A summary of each model, including the number of responses in each UPCR health state at baseline, week 26, and week 52 can be found in the accompanying statistical analysis plan report (Appendix M).

Table 83: Utility linear regression analysis results

Variable	Estimate	P-value
Intercept	0.6180	<0.01
EQ-5D baseline value	0.3852	<0.01
Age	-0.0015	0.02
uPCR > 1 g/g	-0.063	<0.01

Due to the small patient numbers in VALIANT who were categorised as CKD stage 3-5 it was not possible to derive utility estimates for these patients using VALIANT data alone. Therefore, based on available literature, additional utility values for CKD stages 3-5 health states were sourced from Sidhu et al. 2024(28). Utility values from Sidhu et al. 2024 (28) were preferred to other sources used in previous NICE submissions for glomerular diseases (TA1074(134), TA937(141), and TA775(87)) which cited Cooper et al. 2020(159) as the main source. This preference was to prioritise the use of utilities elicited from patients with C3G, instead of CKD.

Table 84: Utility values reported by Sidhu et al. 2024(28)

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

*Mid-point of values from CKD3a and CKD3b patients

Abbreviations: CKD, chronic kidney disease; SE, standard error.

The VALIANT analysis demonstrated an association between uPCR levels and health state utilities. Accordingly, an additional disutility was incorporated into the model for patients with elevated uPCR levels (uPCR > 1 g/g). For CKD stages 1–2, estimates were derived directly from VALIANT. For CKD stages 3–5, where patient numbers in VALIANT were limited, data from Sidhu et al. (2024)(28) were adjusted

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using a disutility of –0.063 from VALIANT analysis (Table 83) allocated to those with uPCR > 1 g/g.

Patients undergoing dialysis are expected to observe worse HRQoL than those without ESRD. A review of the literature did not identify any C3G or IC-MPGN specific utility values for patients undergoing dialysis. As such, values elicited from CKD patients (Cooper et al 2020(159)) undergoing HD and PD were used in the model.

The model also includes the impact of undergoing kidney transplantation on a patients HRQoL. As no utility values for the peri-operative transplant period in C3G or IC-MPGN populations were identified in the literature, an assumption was applied that utility during this period equals that of the lowest utility from the dialysis health states (0.44 for HD), resulting in a utility value of 0.44 for a patient undergoing a transplant. This value is applied for one model cycle whilst a patient is undergoing a transplant. Following transplantation, patients return to the same CKD/uPCR-specific utility values as non-transplant patients, meaning that health state utilities in the model are independent of transplant status.

The utility values used in the analysis are summarised in Table 85.

Table 85: Summary of utility values for cost-effectiveness analysis

Parameter		Utility Value	Source
CKD 1	Remission	0.91	VALIANT
	uPCR <1 g/g	0.91	VALIANT
	uPCR 1 g/g-3 g/g	0.84	VALIANT
	uPCR >3 g/g	0.84	VALIANT
CKD 2	Remission	0.91	VALIANT
	uPCR <1 g/g	0.91	VALIANT
	uPCR 1 g/g-3 g/g	0.84	VALIANT
	uPCR >3 g/g	0.84	VALIANT
CKD 3	Remission	0.75	Sidhu et al. 2024(28)
	uPCR <1 g/g	0.75	Sidhu et al. 2024(28)
	uPCR 1 g/g-3 g/g	0.69	Sidhu et al. 2024(28), VALIANT (uPCR disutility applied)
	uPCR >3 g/g	0.69	Sidhu et al. 2024(28), VALIANT (uPCR disutility applied)

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CKD 4	Remission	0.58	Sidhu et al. 2024(28)
	uPCR <1 g/g	0.58	Sidhu et al. 2024(28)
	uPCR 1 g/g-3 g/g	0.52	Sidhu et al. 2024(28), VALIANT (uPCR disutility applied)
	uPCR >3 g/g	0.52	Sidhu et al. 2024(28), VALIANT (uPCR disutility applied)
CKD 5	Remission	0.58	Sidhu et al. 2024(28)
	uPCR <1 g/g	0.58	Sidhu et al. 2024(28)
	uPCR 1 g/g-3 g/g	0.52	Sidhu et al. 2024(28), VALIANT (uPCR disutility applied)
	uPCR >3 g/g	0.52	Sidhu et al. 2024(28), VALIANT (uPCR disutility applied)
HD		0.44	Cooper et al 2020(159)
PD		0.53	Cooper et al 2020(159)
Undergoing transplant		0.44	Assumption – same as HD utility (Cooper et al 2020(159))

Abbreviations: CKD, chronic kidney disease; HD, haemodialysis; PD, peritoneal dialysis; uPCR, urine protein-creatinine ratio.

Given the limited sample size in Sidhu et al. 2024(28), inconsistencies across utilities for different CKD stages e.g. CKD1 utility being lower than CKD2 utility, and use of EQ-5D-5L (US tariff) data, Cooper et al 2020(159) data were explored in scenario analysis to derive CKD 3-5 utilities.

Age-adjusted general population utility

To estimate health state utilities for the modelled patient populations, age- and sex-adjusted general population utility was first estimated using the algorithm published by Ara and Brazier 2010(161). This was performed to ensure that a decrease in utility over time was incorporated so that utility values were adjusted based on the expected utility decrements associated with ageing. The linear regression model used to estimate the general population utility was:

$$EQ - 5D = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

3.4.5 Cardiovascular event-related disutilities

The model also incorporates a series of cardiovascular event-related disutilities that are applied as a one-off disutility for patients experiencing an event. As such, the model implicitly assumes the disutility associated with each event lasts for one model cycle (3 months). Disutility values used in the model are presented in Table 86.

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Table 86: Summary of disutilities included in the cost-effectiveness analysis

Parameter	Disutility	Sources
MI	-0.06	Guppy et al. (2024)(152)
Stroke	-0.17	Agarwal, et al. 2022(162)
HF	-0.09	McEwan, et. al. 2024(163)

Abbreviations: HF, heart failure; MI, myocardial infarction.

3.5 Cost and healthcare resource use identification, measurement and valuation

3.5.1 Healthcare resource use studies in C3G and IC-MPGN

Relevant cost and healthcare resource utilisation (HCRU) data for patients with C3G or primary IC-MPGN was captured as part of the SLR outlined in section 3.1.

Searches were initially performed in September 2024 with a search cut-off date of 2014. Subsequent updates were conducted in August 2025. The SLR was conducted in accordance with the NICE requirements and CRD guidance. Full details of the SLR search strategy, study selection process and results are presented in Appendix G.

No articles were identified that provided evidence on the cost of C3G and primary IC-MPGN. Two articles reported HCRU in patients with primary C3G or IC-MPGN (49, 164).

In the Adelphi IC-MPGN DSP study(164), over the course of a 12-month period, adults (n = 128) and children (n = 6) with primary IC-MPGN attended a mean of 9.2 appointments: 4.9 of the appointments were with a nephrologist, and 2.1 of the appointments each were with a general practitioner or nurse. To monitor their condition, patients also underwent an average of 25.6 laboratory tests over the 12 months. Following initial diagnostic biopsy, 41% of patients underwent a subsequent kidney biopsy owing to significant proteinuria in 65% of cases. Over the 12 months, 15% of patients had been hospitalised at least once. During the most recent hospitalisation, 56% of patients were admitted to the hospital via the emergency room, with 88% needing to stay overnight. The median duration of hospital stay for these individuals was 4.5 days.

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Length of hospital stay was also reported in a retrospective cohort study conducted by Vasudevan et al. 2022 (49) in India between 2013 and 2020, which found that the mean duration of hospital stay for 43 children with C3G was 16.2 days.

3.5.2 Health-state unit costs and resource use

CKD stage and uPCR category health state costs

The cost of each model health state was estimated using a micro-costing approach, consistent with previous NICE submissions for glomerular disease(134, 141). Given the limited published evidence, expert clinical input was sought to inform the expected annual HCRU for an average patient in each CKD/uPCR health state. This was first elicited through six one-to-one interviews with clinical experts (Section .11), and subsequently validated by additional ad-hoc communications with clinical experts.

Resource use data from the IgAN NICE submission (TA937)(141) were used as a comparator to inform clinician discussions on cost and resource use. The majority opinion was that patients with C3G are likely to require greater healthcare resource use than those with IgAN, partly due to the increased use of immunosuppressants in C3G, which necessitates more frequent monitoring. This was considered particularly relevant for patients in CKD stages 1–3. Clinicians also highlighted that differentiating by proteinuria threshold is more appropriate for C3G than for IgAN, with patients presenting with uPCR levels between 1–3 g/g expected to be reviewed at least every 3 months.

In follow-up communications, one clinician noted that patients with CKD stages 4 and 5 and uPCR >3 g/g would require substantially more intensive monitoring, with outpatient visits and blood tests likely occurring monthly in stage CKD 4, and every 2–4 weeks in CKD stage 5 as patients approach renal replacement therapy.

A breakdown of the HCRU included in the micro-costing analysis is summarised in Table 87.

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Table 87: Annual HCRU and unit costs, by CKD and uPCR health state

	Unit cost	Annual HCRU			Source
		CKD 1-3	CKD 4	CKD 5	
Nephrologist outpatient visits	£209.38				NHS national cost collection (WF01A-D, WF02A-D; Outpatient Care; Renal Medicine; Consultant Led)
Remission		2.00	4.00	4.00	Assumption - Expert clinical feedback
uPCR <1 g/g		3.00	4.00	4.00	
uPCR 1 g/g-3 g/g		4.00	12.00	24.00	
uPCR >3 g/g		6.00	12.00	24.00	
Blood test	£1.46				NHS national cost collection (DAPS; Clinical biochemistry; Chemical Pathology Service;)
Remission		2.00	4.00	4.00	Assumption - Expert clinical feedback
uPCR <1 g/g		3.00	4.00	4.00	
uPCR 1 g/g-3 g/g		4.00	12.00	24.00	
uPCR >3 g/g		6.00	12.00	24.00	
Nurse visits	£141.79				NHS national cost collection (WF01A-D, WF02A-D; Outpatient Care; Renal Medicine; Non-Consultant Led)
Remission		2.00	4.00	4.00	Assumption - Expert clinical feedback
uPCR <1 g/g		3.00	4.00	4.00	
uPCR 1 g/g-3 g/g		4.00	6.00	6.00	
uPCR >3 g/g		6.00	6.00	6.00	
Inpatient visits	£571.82				NHS national cost collection (LA09J-Q; Non-elective inpatient short stay)
Remission		0.50	1.00	2.00	Assumption - Expert clinical feedback
uPCR <1 g/g		0.50	1.00	2.00	
uPCR 1 g/g-3 g/g		1.00	2.00	3.00	
uPCR >3 g/g		2.00	3.00	4.00	

Abbreviations: CKD, chronic kidney disease; HCRU, health care resource use; uPCR, urine protein-creatinine ratio

In the model, unit costs are combined with the annual HCRU values to estimate the average annual cost of treating someone in each of the CKD/uPCR health states. These costs are then adjusted to 3-monthly costs in line with the model's cycle length. A summary of the costs per cycle associated with each CKD/uPCR health state can be found in Table 88.

Table 88: Summary of CKD stage and uPCR health state costs used in the model

Health states/event	Cost per model cycle [£]

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CKD 1	Remission	247.80
	uPCR <1 g/g	335.96
	uPCR 1 g/g-3 g/g	495.59
	uPCR >3 g/g	814.87
CKD 2	Remission	247.80
	uPCR <1 g/g	335.96
	uPCR 1 g/g-3 g/g	495.59
	uPCR >3 g/g	814.87
CKD 3	Remission	247.80
	uPCR <1 g/g	335.96
	uPCR 1 g/g-3 g/g	495.59
	uPCR >3 g/g	814.87
CKD 4	Remission	495.59
	uPCR <1 g/g	495.59
	uPCR 1 g/g-3 g/g	1,131.13
	uPCR >3 g/g	1,274.09
CKD 5	Remission	638.55
	uPCR <1 g/g	638.55
	uPCR 1 g/g-3 g/g	1,906.62
	uPCR >3 g/g	2,049.58

Abbreviations: CKD, chronic kidney disease; uPCR, urine protein-creatinine ratio.

Due to the limited C3G and IC-MPGN specific HCRU or costing literature, and the acknowledgement of the levels of uncertainty associated with expert elicitation of such data, additional scenarios using alternative committee agreed values from previous NICE submissions for glomerular diseases(134) (141) were explored in scenario analysis (Section .9.3).

Dialysis health state costs

Annual dialysis costs are derived from the NHS Schedule of Reference Costs, which provides weighted average unit costs for haemodialysis (delivered in hospital, satellite centres, or at home) and peritoneal dialysis. Haemodialysis costs are based on treatment administered three times per week, equating to 157 sessions per year, while peritoneal dialysis costs are applied daily. Using patient distribution data from activity included in the NHS schedule of reference costs, the model calculates a

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weighted average annual cost of dialysis. This calculation is presented below in Table 89.

Additional costs for procedures associated with the initiation of dialysis (e.g. fistula creation or catheter insertion) are included in the model as a one-off cost when patients transition into the dialysis health state.

Table 89: Dialysis treatment cost

	Unit cost	Annual frequency	Average annual cost	Cost per model cycle	Source
Initiation of haemodialysis	£3,520	One-off cost when initiating dialysis			National Schedule of NHS costs – Year 2023-24 – NHS trust and NHS foundation trusts. Total HRGs - YQ42Z
Haemodialysis	£211	157	£33,171	£8,293	National Schedule of NHS costs – Year 2023-24 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LD01A, LD10A
Initiation of peritoneal dialysis	£1,199	One-off cost when initiating dialysis			National Schedule of NHS costs – Year 2023-24 – NHS trust and NHS foundation trusts. Total HRGs - LA05Z
Peritoneal dialysis	£106	365.25	£38,652	£9,663	National Schedule of NHS costs – Year 2023-24 – NHS trust and NHS foundation trusts. Total HRGs – weighted average LD11A, LD12A, LD13A

Abbreviations: CKD, chronic kidney disease.

Transplant health state costs

Patients in the transplant health state incur annualised costs similar to those in other health states, reflecting ongoing maintenance expenses such as nephrologist visits, blood tests, and immunosuppressive therapy. The cost-effectiveness model includes additional costs of tacrolimus monotherapy (0.25 mg/kg), and two additional nephrologist and GP appointments per year, each accompanied by relevant blood tests.

For new patients entering the transplant state, a one-off procedural cost is applied, covering pre-assessment, the transplant surgery, and post-transplant assessment. This one-time cost is sourced from the NHS Schedule of Reference Costs and is

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applied to all patients upon entering the transplant state. Full details of these costs are provided in Table 90 and Table 91.

Table 90: Transplant procedural costs

	Unit cost	Source
Transplantation preassessment	£461	NHS Schedule of reference costs: LA11Z, LA12A
Transplantation procedure cost	£19,044	NHS Schedule of reference costs: LA01A, LA02A, LA03A
Transplantation posttransplant assessment	£323	NHS Schedule of reference costs: LA13A, LA14Z
Total	£19,827	

Table 91: Transplant maintenance costs

	Unit cost	Annual frequency	Average annual cost	Cost per model cycle	Source
Immunosuppressive therapy - Tacrolimus	£17.83 (Average cost per day)	0.23 mg/kg per day	£6,512	£1,628	SmPC (0.25mg/kg; Mid-point of initial dose minus the fact that ~20% of the SoC basket already includes 0.1mg/kg/day dosing), BNF
GP visit	£45.00	2	£90	£23	PSSRU
Blood test	£1.46	4	£6	£1.46	NHS Schedule of reference costs
Nephrology visit	£209.38	2	£419	£105	NHS Schedule of reference costs: 391 Renal Medicine Service
Hospitalisation	£571.82	0.5	£286	£71	NHS Schedule of reference costs; Non-Elective Inpatient - Short Stay: LA09J, LA09K, LA09L, LA09M, LA09N, LA09P, LA09Q
Total				£1,828	

Abbreviations: GP, general practitioner

Opportunity cost of saved kidneys

The NHSBT “Organ Donation Registry Fact Sheet 7”(165) highlights the substantial cost benefits of kidney transplantation compared to dialysis. Over a period of ten years, which corresponds to the median survival time of a transplanted kidney, the cost-benefit of transplantation is reported as £241,000. This equates to an average saving of approximately £24,100 per year for each year the patient has a functioning transplanted kidney. These savings arise because, while dialysis costs around

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£30,800 annually per patient, transplantation incurs a significantly lower ongoing annual cost, primarily due to reduced treatment and medication expenses after the initial transplant surgery. This substantial long-term cost benefit supports the NHS's efforts to increase transplantation rates for eligible patients with end-stage kidney disease, as it provides considerable financial savings to the healthcare system over the typical lifespan of a transplanted kidney.

The article Axelrod 2018(166) evaluates the health and economic outcomes of kidney transplantation compared to dialysis. A key result of the study is the estimated incremental QALY gain of up to 2.31 QALYs for patients receiving a transplant instead of remaining on dialysis. The study emphasises that kidney transplantation not only offers significant cost savings but also provides substantial health benefits, confirming its value as the preferred treatment option for eligible patients with end-stage kidney disease.

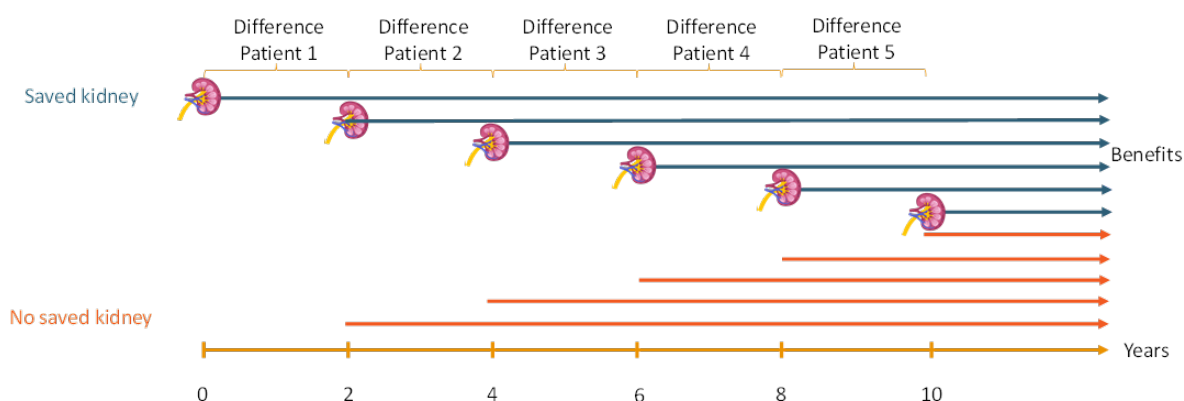
The above data sources provide estimates of the cost savings and QALYs gained from a single additional kidney transplant benefiting patients with ESKD on the transplant waiting list. Both sources use a 10-year time horizon, so these estimated benefits can be applied in cost-effectiveness models only if it is reasonable to assume that one additional kidney transplant results in 10 years of dialysis time saved. This assumption is supported by NHS data, which identifies the 10-year time horizon as the median survival time of a transplanted kidney. Since the median survival time is typically shorter than the mean survival time, adopting a 10-year benefit duration can be considered a conservative estimate.

It should be understood that the full 10-year benefit will not be realised by a single patient, as the time a patient spends on dialysis is typically around the average waiting time for a transplant, which is slightly over 2 years. However, regardless of the time saved for one patient, this reduction in dialysis time is effectively transferred to another patient on the waiting list. Since kidneys are a scarce resource and demand consistently exceeds supply, there will always be patients on the waiting list who benefit from the time saved due to a single additional kidney becoming available. Therefore, it can be concluded that the total cumulative savings will

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exceed the assumed 10-year time horizon. This concept is illustrated graphically in Figure 20.

Figure 20: Opportunity cost time horizon



Following expert consultations, the above concept was strengthened by more robust modelling of the waiting time for a kidney transplant using a separate queuing model.

Queuing model

Queueing models are mathematical tools designed to analyse systems in which individuals compete for access to limited resources, such as organs available for transplantation. In the context of transplant medicine, they enable the formal modelling of allocation processes, simulation of transplant waiting lists, and evaluation of alternative organ distribution strategies. These models account for key variables such as waiting time, medical urgency, and immunological compatibility. They form the foundation for designing, assessing, and comparing allocation policies prior to clinical implementation, thereby promoting more transparent and data-driven decision-making.

Queueing systems are typically classified based on characteristics such as arrival patterns (e.g., Poisson processes), number of servers (e.g., single vs. multi-channel), service rules (e.g., first in first out [FIFO], priority-based), and service time distributions. In transplantation, priority-based models are especially relevant, as they allow dynamic reordering of the queue based on clinical indicators. Depending on the level of detail required, both analytical models and simulation-based

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approaches can be used. Among them, the M/M/c (Markovian arrivals/ Markovian service times/ servers) priority model is the most employed as a foundational framework (167). The M/M/c model assumes that customers arrive according to a Poisson process, and service times are independent and exponentially distributed. The system includes c parallel servers, each serving one customer at a time, while others wait in a FIFO queue.

The problem of kidney transplantation is well captured by the model proposed by Zenios 1999(168), which realistically reflects the dynamics of waiting for a transplant under organ scarcity and patient heterogeneity. The model applies an M/M/ ∞ (∞ stands for organ supply) multiclass queue with reneging. This publication remains one of the most widely cited applications of queueing theory in transplant medicine. It incorporates both patient and organ heterogeneity, as well as the reneging, i.e., patients exiting the queue before receiving a transplant. The derived asymptotic expressions provide valuable insight into the impact of allocation policies and mortality on system performance, establishing the model as a robust benchmark for further dynamic analyses and ethical evaluations of organ allocation.

For the purposes of this cost-effectiveness model, an independent queueing model was developed in accordance with the assumptions outlined by Zenios, with input data sourced from the NHS Organ and Tissue Donation and Transplantation Activity Report 2023/2024(78). The primary objective was to validate the Zenios queueing model using real-world data and subsequently apply the model to assess the impact of reducing transplant demand.

The average waiting time for kidney transplantation in the UK was estimated using NHS data. The proportion of patients receiving a kidney transplant was calculated based on registration outcomes for 3,502 new adult kidney-only registrations made in the UK between 1 April 2018 and 31 March 2019. It was determined that approximately 44% of recipients waited less than one year, 31% waited between one and three years, 14% between three and five years, and 11% more than five years.

To estimate the average waiting time, the midpoints of each time interval were used, with seven years assigned to the final category. Based on this approach, the average waiting time was calculated to be approximately 2.18 years.

In the model assumptions, the annual kidney supply was defined as the number of transplants performed between 1 April 2023 and 31 March 2024, which totalled 2,448. To estimate the system load (p) we used an equation derived from Zenios model: $p = \frac{\lambda^+}{\lambda^-}$, where λ^+ represents the number of new patients added to the transplant waiting list in 2024, and λ^- corresponds to the kidney supply in the same year.

The number of new patients was calculated as the difference between the 2024 and 2023 waiting list sizes, adjusted for transplants performed:

6,250 (2024 list size) – 5,655 (2023 list size) + 2,448 (transplants) = 3,043 new patients.

Substituting these values, the system load was estimated at $p = 3,043 / 2,448 = 1.24$.

In 2023, a total of 265 patients died while on the kidney transplant waiting list. Based on data from the NHS report (Table 92), an additional assumption was incorporated: patients waiting less than three years were assumed to have an equal probability of leaving the queue due to death or other non-transplant reasons. This assumption effectively doubled the number of individuals exiting the queue from 265 to 530. Accordingly, the reneging rate was calculated as 530 out of 5,655 patients, resulting in a rate of 9.37%.

Table 92: NHS Organ and Tissue Donation and Transplantation Activity Report

Year	On waiting list	Kidney supply	Deaths
2023	5,655	2,350	281
2024	6,250	2,448	265

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Substituting these parameters into the formula provided by Zenios 1999 (168) yielded an estimated average waiting time of 2.3215 years, closely aligning with the 2.18 years calculated directly from NHS data. While not a perfect match, this level of agreement was deemed sufficient for model validation.

Subsequently, a similar calculation was performed with the demand reduced by one patient, simulating a scenario in which one fewer individual requires a transplant. Under this condition, the estimated average waiting time was 2.318 years (Table 93).

Table 93: Queuing model estimates

Average waiting time		
NHS data	Zenios model	
	Demand = 3,043	Demand = 3,042
2.1780	2.3215	2.3180

Although the difference in average waiting times is minimal (0.0035 years $\approx$ 1.3 days), the reduction in demand translates into a total savings of over 10 cumulative years in the transplant queue across all patients (1.3 days saved on average for 3,043 new patients results in a cumulative saving of 10.6505 years).

The results of the analysed queuing model should be interpreted with caution, as the model inputs were based on NHS data that did not directly specify all model parameters. Nevertheless, validation of the model against the actual mean time to kidney transplant is encouraging. Importantly, the key finding, largely independent of the exact model outputs, is that even a seemingly small reduction in the demand for kidney transplants can lead to a substantial decrease in the total time patients spend on dialysis. The total time saved on dialysis across the whole NHS system is likely to exceed the 10-year benefit duration; therefore, the cost-effectiveness model assumes each transplant avoided results in 10.6505 years of QALY gains and costs savings across the NHS.

3.5.3 Intervention and comparators' costs and resource use

Intervention and comparator costs are incurred by all patients throughout the model time-horizon, with 100% assumed adherence, except in two instances:

1. A patient has discontinued treatment due to safety concerns – as identified in VALIANT (Section .3.6)
2. A patient has improved to the point whereby they are considered to have stable disease (Section 3.3.3).

The 100% adherence assumption is likely to overestimate acquisition costs of pegcetacoplan due to the typically lower adherence in real-world use than in a controlled clinical trial setting.

Pegcetacoplan

Pegcetacoplan is administered twice weekly as a 1,080mg subcutaneous infusion with a commercially available syringe system infusion pump that can deliver doses up to 20 mL. The twice-weekly dose should be administered on Day 1 and Day 4 for each treatment week.

Table 94: Pegcetacoplan treatment acquisition costs

	Vial size (mg)	List Price	Dose required (mg)	Administrations per model cycle (13.04 weeks)	List price per model cycle	PAS	Net price per model cycle
Pegcetacoplan	1,080	£3,100	1,080	26.09	£80,877		

Pegcetacoplan is assumed to be self-administered subcutaneously by all patients, therefore, no costs associated with administration were included in the model.

Standard of care

The treatments included in the model for standard of care (SoC), along with their respective usage proportions, are detailed in Table 63 (Section .3.2). The associated costs for each intervention included in the base-case SoC are summarised in Table 95. The model estimates the average cost per treatment category, assuming an even share of formulation (see Appendix I for details) and calculates a weighted 3-Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

monthly average cost for each category based on their relative use in the randomised period of the VALIANT trial. A scenario observing the use of distributions from the open-label period of VALIANT is also explored within the model. These weighted costs are then aggregated to derive the total 3-monthly SoC cost per model cycle.

Drug acquisition and vial costs for all included interventions were sourced from the British National Formulary (BNF)(169) and the drugs and pharmaceutical electronic market Information Tool (eMIT) National Database January 2024 to December 2024 (170), which provides information about prices and usage for generic drugs and pharmaceutical products. For treatments with multiple vial or pack sizes, a simple average of 3-month costs for each vial or pack size was used. Where multiple brands of the same vial or pack size were available the least costly was used.

Table 95: SOC treatment basket drug acquisition costs

Treatments included in SoC basket	Valiant randomised period relative usage	Weighted 3-monthly average cost
ACEi/ARB		£10.01
Immunosuppressants		£140.60
Systemic corticosteroids		£37.20
SGLT2i		£23.10
Total		£210.90

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB; angiotensin receptor blockers; OLP, open-label period; SGLT2i; sodium-glucose cotransporter-2 inhibitor; SoC, standard of care

Iptacopan

Iptacopan is administered orally at a recommended dose of 200 mg twice daily. It is supplied as hard capsules containing 200 mg of the active substance. Treatment is continuous and not dependent on body weight or titration. Iptacopan is available in packs of 56 capsules.

Table 96. Iptacopan treatment acquisition costs

	Price per pack	Units per pack	Price per unit	Frequency	Administrations per model cycle (13.04 weeks)	Cost per model cycle
Iptacopan	£26,500	56	£473.21	Twice a day	182.56	£86,420.76

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Iptacopan is assumed to be self-administered by all patients; therefore, no costs associated with administration were included in the model.

3.5.4 Adverse reaction unit costs and resource use

Due to the exclusion of adverse events within the cost-effectiveness model, no associated costs have been included.

3.5.5 CV event and mortality event costs

The costs modelled for each CV event and mortality occurring in the model were identified from available literature. The cost of each CV event and death was included in the model as a one-off cost at time of CV event or death occurrence. The associated sources for each cost, are detailed in Table 97.

Table 97: CV event model costs

Events		
MI	£9,280	Alva, The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84) (171)
Acute Stroke	£9,900	
Post-Stroke	£371	
Heart Failure	£4,643	
CV – Mortality	£11,382	PSSRU 2023 (172), updated to UK 2025
Renal Death	£11,382	

Abbreviations: CV, cardiovascular; MI, myocardial infarction.

3.6 Severity

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

3.7 Uncertainty

As outlined in Section .3.1, there is a large body of evidence supporting the use of proteinuria reduction and stabilisation or improvement of eGFR as surrogate endpoints for predicting renal outcomes in patients with chronic kidney disease. For these reasons, uPCR and eGFR levels were used to define health states. This decision was further supported by feedback from clinicians on the advisory board, who agreed that lower uPCR is associated with reduced rates of disease

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progression (Section .11). However, it remains unclear whether additional explanatory variables influencing CKD progression may exist but have not yet been identified in glomerular disease research, and as a result, these could not be incorporated into the model.

3.7.1 Assumptions

A list of the assumptions made in the base-case analysis and their justifications is provided in Table 98.

Table 98: Summary of assumptions used in the analysis

Model Input	Description of assumption	Justification	Reference to the section in the submission
Time horizon	Lifetime (max age 100 years)	C3G and IC-MPGN are lifelong; lifetime horizon captures full benefit of treatment	Section .2.2, Table 62
Cycle length	3 months	Appropriate to capture CKD transitions while minimising variability from short-term eGFR fluctuations	Section .2.2, Table 62
Half-cycle correction	Applied	Consistent with NICE reference case	Section .2.2, Table 62
Discounting	3.5% for costs and utilities	NICE reference case requirement	Section .2.2, Table 62
Baseline distributions	Patients distributed by CKD stage/uPCR from VALIANT	Ensures efficacy data from VALIANT reflects model population	Section .2.2, Table 61
Disease progression	eGFR decline varies by uPCR; <1 g/g assumed no decline	Based on VALIANT regressions. Extrapolation of eGFR improvements in the long-term was not deemed to be clinically plausible	Section .2.1 – .3.2
Stable disease	Patients achieving uPCR <1 g/g can pause treatment until relapse	Supported by clinical expert opinion received during advisory board and interviews.	Section 3.2.2
Treatment discontinuation	1.65% per cycle	From VALIANT data: 6 patients discontinued; assumption applied across cycles and treatments due to limited alternative data	Section .3.6
Adherence	100%	Adherence in the clinical trial was high. This assumption ensures the treatment acquisition costs align with the health outcomes from the trial. However, this may be conservative relative to real-world use due to the typically higher adherence in a controlled clinical trial settings.	Section .5.3

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Treatment waning	None	VALIANT + PNH data show sustained C3 inhibition; no evidence of waning based on clinical expert opinion	Section .3.6
Dialysis initiation	100% of CKD5 patients move to dialysis after 1 cycle	Reflects rapid requirement of RRT (within 3-months) once a patient reaches CKD5	Section .3.2
Dialysis modality	88% HD / 12% PD	Based on UK Renal Registry data	Section .3.2
Dialysis costs	Annual dialysis costs from NHS reference costs (LD HRGs). Surgical access included	This source aligns with NICE methods	Section .5.2
Transplant probability	13.45% per cycle (median 14.4 months wait); graft survival 95.32% first cycle	Based on robust UK renal registry data & most relevant source in the current literature (Pruett 2021)	Section .3.2
Transplant utility	Equal to HD utility	Due to a lack of data in the literature patient HRQoL is assumed to be as worse as the lowest HRQoL health state (HD)	Section .4.4
Mortality	ONS life tables adjusted with CKD/dialysis HRs	Supported by Quist 2025(155); conservative assumption (constant risk post-renal failure)	Section .3.5
Utilities (CKD/uPCR)	Sidhu et al. 2024 + VALIANT disutility for high uPCR	Using only known disease specific utility values from the literature for later CKD stages (3-5), due to limited sample size in these CKD stages in VALIANT. VALIANT EQ-5D data used, in line with NICE reference case, for patients in CKD stage 1-2.	Section .4.4
eGFR decline in stable disease	Excluded	Patients in stable disease will have similar kidney deterioration to those with low (<1 g/g) uPCR.	Section .3.2
SOC basket proportions	From VALIANT randomised period	Reflects concomitant medications observed in the trial	Section .2.3
Costs	CKD, dialysis, transplant from NHS reference costs; AEs excluded	Consistent with NICE reference case. Treatment related AEs that are likely to incur costs borne by the healthcare service were observed in less than 5% of patients, so were not deemed to have an influential impact on the model results.	Section .5
Surrogate endpoints	uPCR and eGFR defined health states	Strong predictors of renal outcomes, supported by published evidence	Section .3.1
Opportunity cost of saved kidney	10.6505 years dialysis avoided per transplant	Additional analysis using NHS transplant registry and queuing model indicates there are additional benefits across the wider NHS from avoiding a transplant.	Section .5.2

Abbreviations: AE, adverse event; CKD, chronic kidney disease; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; HD, haemodialysis; HR, hazard ratio; HRG, healthcare resource group; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; NCC, National Cost Collection; NHS, National Health Service; ONS, Office for National Statistics; PD, peritoneal dialysis; PNH, paroxysmal nocturnal

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haemoglobinuria; RRT, renal replacement therapy; SLR, systematic literature review; SoC, standard of care; uPCR, urinary protein-to-creatinine ratio.

3.8 Base-case results

Summary

- In the base-case, the incremental cost-effectiveness ratio (ICER) for pegcetacoplan vs standard of care is £28,714/QALY, which represents [REDACTED] incremental QALYs and [REDACTED] incremental costs.
- Pegcetacoplan vs iptacopan resulted in a dominant cost-effectiveness outcome (higher QALY gain for lower costs), represented by [REDACTED] incremental QALYs and [REDACTED] incremental costs.

3.8.1 Base-case incremental cost-effectiveness analysis results

The deterministic base-case cost-effectiveness analysis results over a lifetime horizon are summarised in Table 99.

Table 99: Base-case deterministic results (PAS price)

	Pegcetacoplan	Standard of care	Iptacopan
Total			
Costs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
LYs	47.236	40.520	43.468
Incremental			
Costs		[REDACTED]	[REDACTED]
QALYs		[REDACTED]	[REDACTED]
LYs		6.715	3.768
Cost-effectiveness			
ICER (£/QALY)		£28,714	Dominant
NHB (at £20,000/QALY)		-3.165	98.236
NHB (at £30,000/QALY)		0.311	66.359
Fully incremental ICERs			
Versus referent	£28,714	Referent	Dominated
Versus next least costly	£28,714	Referent	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years

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3.9 Exploring uncertainty

3.9.1 Probabilistic sensitivity analysis

A Monte Carlo style probabilistic sensitivity analysis (PSA) was conducted on the model, varying all the parameters indicated in Table 151 (Appendix K), as well as the transition matrices used. The PSA was performed for 1,000 iterations. Distributions and confidence intervals of each parameter included in the PSA can be found in Appendix K. Table 100 provides a comparison between the base case deterministic results and the average results of the PSA. Figure 21 illustrates the cost-effectiveness plane for the PAS price. Figure 22 illustrates the cost-effectiveness acceptability curve illustrating that pegcetacoplan has a [REDACTED] % probability of being cost-effective at a £30,000/QALY willingness to pay threshold.

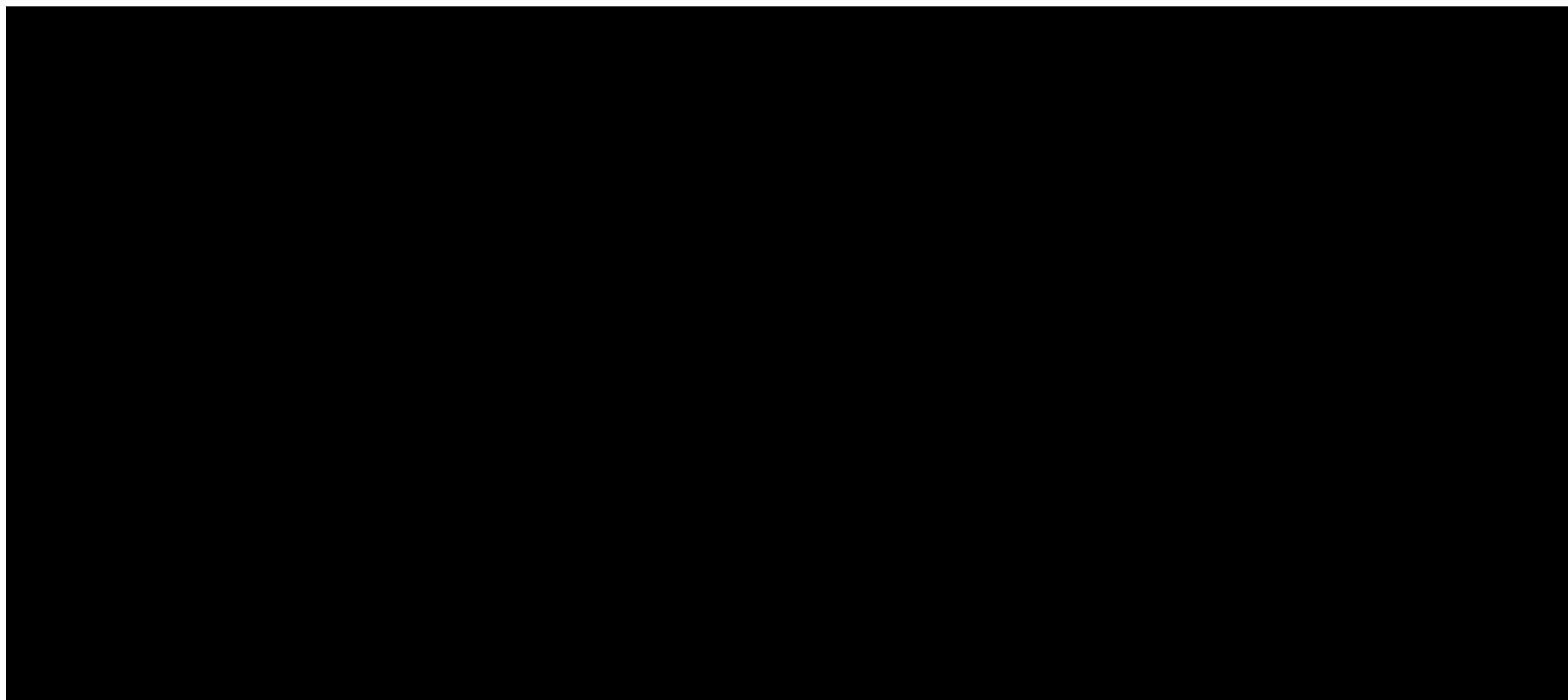
Table 100: Comparison between probabilistic and deterministic results (1,000 iterations)

	Total		Incremental		Cost-effectiveness	
	Cost	QALY	Cost	QALY	ICER (£/QALY)	NMB (£) at £30,000/QALY
Deterministic result						
Pegcetacoplan	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		
Standard of Care	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£28,714	£9,343
Iptacopan	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant	£1,990,769
Probabilistic result						
Pegcetacoplan	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		
Standard of Care	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£50,571	-£144,548
Iptacopan	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant	£1,960,462

Abbreviations: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.

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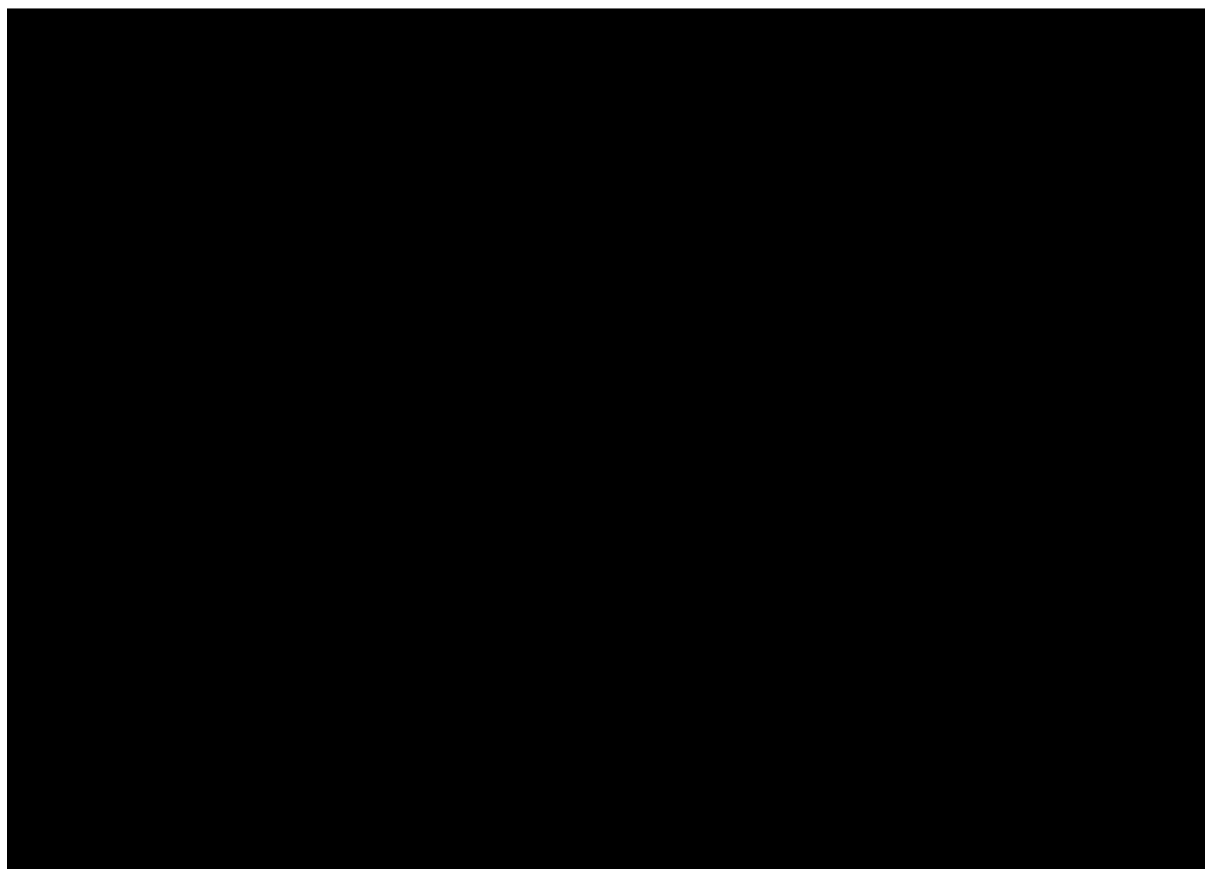
Figure 21: Cost-effectiveness plane



Abbreviations: NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness to pay

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Figure 22: Cost-effectiveness acceptability curve



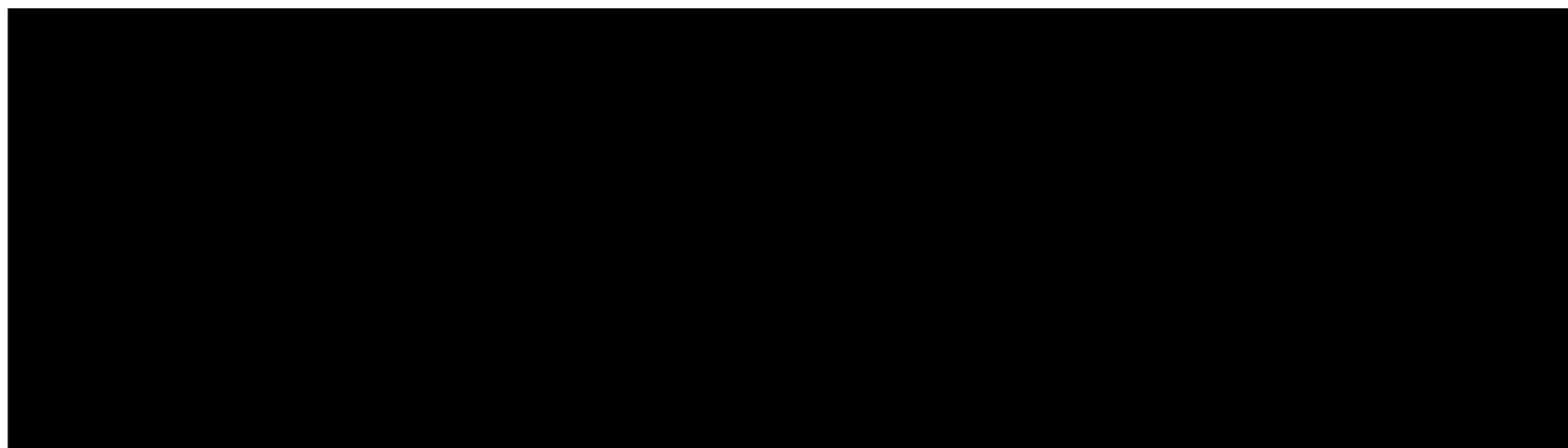
3.9.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted to assess the sensitivity of individual parameters on the model results. A full list of varied parameters is described in Table 151 (Appendix K). Tornado plots illustrating the 10 most impactful parameters for pegcetacoplan vs SOC and pegcetacoplan vs iptacopan are provided below in Figure 23 and Figure 23, respectively.

For the comparison with SOC, the most influential parameter was the probability of disease remission from the uPCR <1 g/g state for pegcetacoplan. The second most impactful parameter was the probability of disease relapse after remission for pegcetacoplan. Following this, the cost of a saved kidney was the next most impactful parameter.

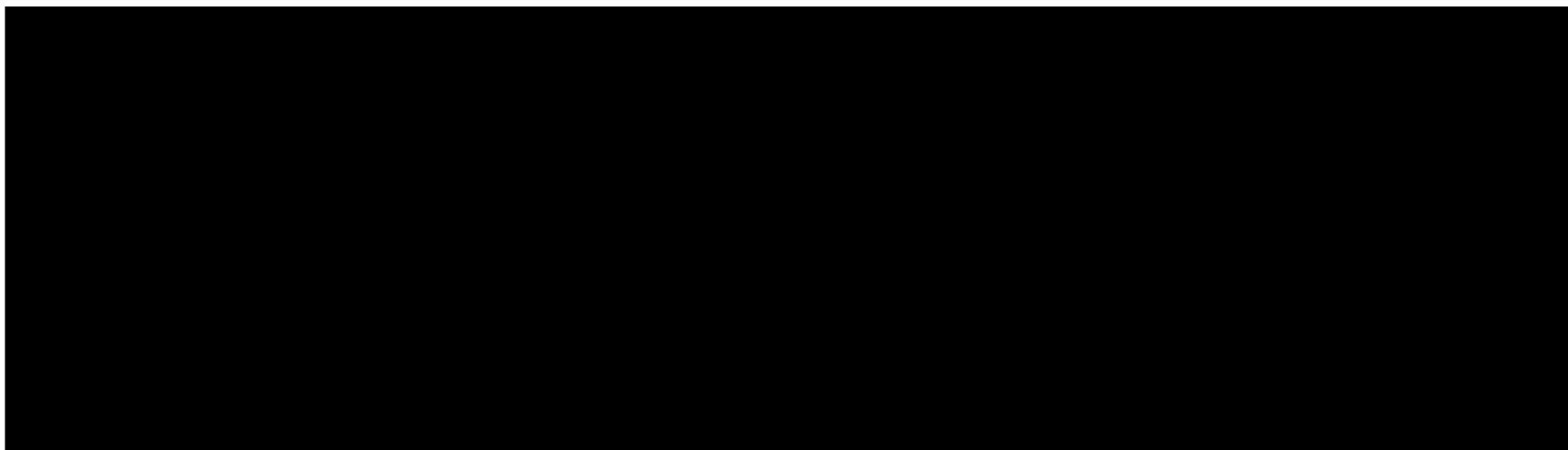
For the comparison with iptacopan, the ten most influential parameters focused on utilities associated with the remission health state, discontinuation rates, QALY value of a saved kidney, and movement in and out of the stable disease health state.

Figure 23: Tornado plot of most impactful parameters on the ICER vs SOC



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, haemodialysis; SOC, standard of care; UPCR, urine protein-creatinine ratio
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Figure 24: Tornado plot of most impactful parameters on the ICER vs iptacopan



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, haemodialysis; QALY, quality adjusted life year; SOC, standard of care; UPCR, urine protein-creatinine ratio

3.9.3 Scenario analysis

Summaries of all the scenarios evaluated are provided in Table 101. The results of the model based on these different scenarios are provided in Table 102.

Table 101: Description of scenarios evaluated

Scenario #	Variable	Base case	Scenario	Description
1	uPCR state and eGFR stage transitions informed by VALIANT	52-week data in pegcetacoplan arm; 26-week data in placebo arm	26-week VALIANT data used in both arms	To align the time horizon of the data used in each arm of the model, this scenario only uses data from the randomised period of the VALIANT trial
2	eGFR decline for those in stable disease	No decline in eGFR	-0.18 mL/min/1.73 m ² decline per 3-month cycle (Guppy et al. 2024)	To assess the impact of assuming continued eGFR decline for patients with stable disease
3	Graft survival	Pruett et al. 2021: 95.32%	Masoud et al. 2025: First transplant: 98.57% Subsequent transplant: 97.84%	To assess the use of alternative estimates for the improved survival of grafts following a transplant.
4	uPCR/CKD health state utility	CKD stages 1-2: VALIANT CKD staged 3-5: Sidhu et al. 2024 (140) with decrement applied for patients with uPCR > 1g/g based on VALIANT data analysis	CKD stages 1-2: VALIANT CKD staged 3-5: Cooper et al. 2020 with decrement applied for patients with uPCR > 1g/g based on VALIANT data analysis	To assess impact of alternative source of utility based on findings in CKD patients that have been used in previous NICE appraisals(134, 141)
5	uPCR/CKD health state utility	CKD staged 3-5: Sidhu et al. 2024 (140) with decrement applied for patients with uPCR > 1g/g based on VALIANT data analysis	CKD staged 3-5: Adjusted Sidhu et al. 2024 (140) figures to account for difference in age versus model base case. Decrement applied for patients with uPCR > 1g/g based on VALIANT data analysis	To assess impact of re-weighting Sidhu et al utility values to ensure they align me to the age of the model population
6	uPCR/CKD health state costs	Micro-costing analysis	Costs, by CKD stage only, obtained from previous NICE appraisal (TA937)	To assess the impact of alternative HCRU estimates from previous NICE

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				appraisals in other glomerular disease.
7	SOC basket: relative usage of treatments	VALIANT randomised period	VALIANT open-label period	To assess the impact of changing the relative usage of each treatment in the SOC basket based on the different periods in the VALIANT trial
8	SOC basket: treatment costs	Even usage of different formulations	Least expensive formulation used	To assess the impact if only the least expensive SOC in each treatment class was used for the SOC basket.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HCRU, healthcare resource use; SOC, standard of care; uPCR, urine protein-creatinine ratio

Table 102: Results of scenarios

Scenario		Scenario results (incremental)						Difference from base case					
		Costs (£)		QALYs		ICER (£/QALY)		Costs (£)		QALYs		ICER (£/QALY)	
		SOC	Iptacopan	SOC	Iptacopan	SOC	Iptacopan	SOC	Iptacopan	SOC	Iptacopan	SOC	Iptacopan
Base case	-					28,714	Dominant						
uPCR state and eGFR stage transitions informed by VALIANT	1					18,266	Dominant					-10,448	No change in dominance
eGFR decline for those in stable disease	2					31,765	Dominant					3,051	No change in dominance
Graft survival	3					30,244	Dominant					1,530	No change in dominance
uPCR/CKD health state utility source	4					31,590	Dominant					2,876	No change in dominance
uPCR/CKD health state utility age adjustment	5					29,115	Dominant					401	No change in dominance
uPCR/CKD health state costs	6					31,058	Dominant					2,345	No change in dominance
SOC basket: relative usage of treatments	7					28,732	Dominant					18	No change in dominance
SOC basket: treatment costs	8					28,872	Dominant					159	No change in dominance

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3.9.4 Subgroup analysis

Subgroup analyses in VALIANT (section and Appendix C) showed consistent treatment effects across C3G and IC-MPGN, adults and adolescents, and post-versus non-transplant patients, with no statistically significant differences observed in key proteinuria and eGFR results. Given this consistency, and recognising the rarity of the conditions and limited subgroup sizes, subgroup analyses are not expected to significantly impact the economic analysis either.

3.10 Benefits not captured in the QALY calculation

Caregiver burden

C3G and IC-MPGN frequently present earlier in life than many other chronic kidney diseases, with diagnoses reported in childhood and adolescence. In the VALIANT trial, 44.4% of patients in the ITT population were adolescents aged 12–17 years, including 60.7% of patients in the IC-MPGN subgroup and 26.9% of patients in the C3G subgroup(146).

Early onset has important implications, as the conditions can disrupt education, limit long-term career development, and increase lifetime productivity losses, none of which are captured within the QALY framework. Furthermore, early disease onset places a significant burden on caregivers, particularly parents of adolescent patients, who are responsible for managing treatment, coordinating medical care, and supporting psychosocial wellbeing over many years. For example, Children under the age of sixteen require a chaperone in hospital transport. Therefore, the younger the child is at when progressing to ESRD, the greater number of days of dialysis required, and the additional burden on caregivers. Due to the potential frequency with which children require dialysis, around four to five days a week, it is difficult for caregivers to also maintain a career. This can lead to short-term financial implications (e.g. reduced income, increased costs [e.g. food to help the child maintain a good renal diet, additional cleaning supplies to prevent infections around catheters/lines, utility bills if undergoing home dialysis]) and long-term financial implications (e.g. reduced opportunity to pay into pension, greater reliance on credit Company evidence submission for pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

or loans). While welfare benefits can offer some support, they rarely compensate fully for lost income. Accessing these benefits also carries an administrative burden, demanding time and resources that caregivers often already lack.

These caregiver responsibilities and broader societal impacts are not we explored in existing literature. Therefore, these additional burdens are not reflected in the modelled health outcomes, but represent meaningful benefits of effective treatment.

Paediatric patients' healthcare resource use and cost

Feedback from paediatric nephrologists collected during the clinician interviews outlined in Section .11 indicated that paediatric patients typically require additional healthcare resources. In particular, those with CKD stage 4–5 would receive psychology, play therapy, and dietitian input. Dietitian and play therapy support would usually occur at the same frequency as outpatient visits, while psychology input would typically consist of one to two visits per year.

To avoid additional complexity, the current model does not differentiate health-state unit costs or resource use between paediatric and adult patients. As a result, potential cost savings from improved outcomes in paediatric patients are not explicitly captured and therefore represent an additional potential saving from treatment with pegcetacoplan not reflected in the model.

Kidney failure risk of death assumption

Evidence from the literature suggests that there is an increased risk of death in the first 3-6 months following kidney failure(33-36). Despite this, the current model for pegcetacoplan adopts a conservative assumption that the risk of death among individuals with kidney failure remains constant over time. This approach was taken to maintain simplicity and transparency in the model and to avoid the additional complexity that would arise from introducing tunnel states. As a result, potential QALY gains from reducing early mortality following kidney failure are not captured within the current model.

3.11 Validation

3.11.1 Validation of cost-effectiveness analysis

The model was developed based on clinical insights gathered from nephrologists during an advisory board convened by Sobi in April 2024, and through a series of follow-up interviews conducted in May 2025. The advisory board included nine nephrologists, and an additional six interviews were held with nephrologists. All participating clinicians routinely managed patients with C3G and IC-MPGN and are based at a representative selection of centres across England. For full details of the advisory board and clinician interviews see Appendix L.

The advisory board validated the following key model assumptions;

- Generalisability of results from VALIANT to the economic model population
- Relationship between uPCR levels and eGFR
- Health state quality of life utilities
- Model health states uPCR cut-offs
- Model cost drivers and considerations
- Model transplant assumptions
- Treatment stopping rules/discontinuation

The additional clinical expert interviews further validated the following key model assumptions:

- Relationship between uPCR and eGFR
- Health state quality of life utilities
- eGFR decline assumptions
- Spontaneous remission
- Model transplant assumptions
- Treatment stopping rules/discontinuation
- Criteria for restarting treatment
- Costing and resource use
- C3G primary IC-MPGN modelling comparability

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Based on the findings, the model was updated where necessary. The results of the validation are reported in Appendix L.

Validation of the model programming was conducted by a secondary health economist to ensure the accuracy of all input parameters and the correctness of the calculations used within the model. This review process aimed to eliminate potential errors and confirm that the model was implemented according to the intended methodological framework.

Additional expert HEOR elicitation was sought to inform the model design, including the incorporation of the opportunity cost framework for assessing the potential wider system impact of a reduced need for kidney transplants following the introduction of pegcetacoplan (Appendix N).

External validation against other published economic evaluations was not considered feasible, as no existing cost-effectiveness models were identified for any treatment within IC-MPGN or C3G.

3.12 Interpretation and conclusions of economic evidence

C3G and primary IC-MPGN are complement-mediated glomerular diseases distinguished by the presence or absence of underlying immune complexes but united by aberrant complement pathway activation. They are rare diseases affecting children and adults, often progressive and challenging to treat. Traditional treatments (corticosteroids, cytotoxic or other immunosuppressives) have shown limited success.

Pegcetacoplan treatment impacts disease progression by reducing uPCR levels, which slows the decline in eGFR and delays advancement through CKD stages. Furthermore, patients receiving pegcetacoplan have a higher probability of disease stabilisation compared to those on standard care, due to achieving lower uPCR levels and a greater proportion reaching uPCR <1 g/g. Consequently, these patients spend less time in advanced CKD stages and on dialysis, resulting in both cost savings and improved QALYs.

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The economic value of pegcetacoplan was evaluated using a Markov model approach to demonstrate the movement of patients through health states defined by UPCR, eGFR, dialysis, transplant, and death. The model structure expanded on previous models in CKD and other glomerular diseases with the inclusion of the impact of proteinuria on delaying time to renal replacement therapy.

The current base-case provided long-term estimates of people suffering with the chronic conditions, C3G and primary IC-MPGN. The model estimated discounted LY benefit of 6.715 and 3.768, and a discounted QALY benefit of [REDACTED] and [REDACTED] for pegcetacoplan compared to SOC and iptacopan, respectively. The total discounted cost difference was estimated at around [REDACTED] and [REDACTED], with a discounted ICER of £28,714/QALY for the comparison with SOC and a dominant ICER (higher QALYs with lower costs) for the comparison with iptacopan. These results suggest a meaningful extension in both the quantity and quality of life for this very limited patient population with significant unmet need, highlighting the potential value of pegcetacoplan from a public health perspective.

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Single technology appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Summary of Information for Patients (SIP)

September 2025

File name	Version	Contains confidential information	Date
ID6489 Pegcetacoplan iv. NICE SIP	1.0	No	4 September 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Pegcetacoplan (brand name: ASPAVELI)

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

Pegcetacoplan is indicated to treat adult and adolescents, aged 12 to 17 years, with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN).

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

Pegcetacoplan has submitted an application for marketing authorisation, which is currently pending. Anticipated approval dates in the UK and Europe are included in section 1.2 of the company submission.

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

Sobi has engaged with patient groups relevant to the medicine, including providing Kidney Research UK with £15,000 for membership of their industry partnership programme.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

C3G and primary IC-MPGN are rare and seriously debilitating chronic kidney diseases, that primarily affect children and young adults. (1). The estimated prevalence in Europe is 1.3 cases per 10,000 population (2) and in the UK the prevalence of C3G and primary IC-MPGN is estimated at 2.0 per million and 2.2 per million, respectively which equates to approximately 110 C3G and 124 primary IC-MPGN patients in England and Wales.(3, 4)

In both diseases, an important part of the immune system known as the complement cascade is overactive, which results in the excessive breakdown of a protein called C3. (5) These C3 breakdown products become trapped in the kidney, causing inflammation and damage to the organ. (6)

C3G and primary IC-MPGN present with a wide range of symptoms, some of which are undetectable in the early stages. (1, 7) Common symptoms include haematuria (blood in the urine), proteinuria (protein in the urine) and nephrotic syndrome (large amounts of protein in the urine, causing fluid retention and swelling). (1, 8) Some patients also experience non-kidney related symptoms such as lipodystrophy (abnormal fat distribution in the body), oedema (swelling due to a buildup of fluid in the body's tissues), and retinal issues (the retina is the light-sensitive layer of tissue at the back of the eyeball). (7, 9) In more severe cases, over 5% of patients develop a rapidly progressing form of kidney disease, called crescentic glomerulonephritis, which accelerates to progressive kidney damage. (10, 11)

People affected by C3G and primary IC-MPGN face a significant unmet need. These rare diseases can lead to kidney failure within five to ten years of diagnosis, requiring patients to go on dialysis or get a kidney transplant. (12) Additionally, 80% of patients who previously received a kidney transplant will experience recurrence of their disease. (13) Before this, the decline in kidney function is associated with worsening symptoms, such as fatigue (tiredness), hypertension (high blood pressure) and oedema (swelling), all of which significantly impact patients' quality of life (QoL). (14) Without effective treatment, this decline continues, with up to 70% of patients requiring dialysis and/or multiple kidney transplants. (15, 16) This rapid progression, along with its early onset, sets this condition apart from other chronic kidney diseases. (17)

C3G and IC-MPGN are associated with physical and mental burden. (14, 18) In a large study which examined quality of life (QoL) and fatigue in patients with C3G (14) patients experienced debilitating fatigue (91–93%), mobility issues (42%) and a significant decline in overall QoL, with 63% of patients struggling with daily activities. This study also highlighted the mental burden on patients, with 74% reporting anxiety and depression. Children frequently experience extended hospital visits, leading to missed school and disrupted education, while adults struggle to maintain employment. (18)

For patients with C3G and primary IC-MPGN unable to receive a transplant or awaiting a donor kidney, dialysis is a necessary but exhausting treatment. In the UK, patients on dialysis typically wait around three years for a transplant, though some may die waiting, or be removed from the list due to deteriorating health. (19) Even for patients who receive successful kidney transplants,

the psychological burden remains significant. (20) Lifelong immunosuppressive medications, essential to prevent graft rejection, not only exposes patients to an increased risk of infections but also heightens their susceptibility to certain cancers. (21)

Mortality rates for C3G and primary IC-MPGN are comparable and may be as high as 21% for C3G (22-25) and 11–21% for IC-MPGN. (22, 23, 25, 26) In a longitudinal study of 1,089 patients with C3G and primary IC-MPGN, 54% of patients progressed to end stage kidney disease (kidneys are only functioning at 10–15% of their normal capacity) and 14% died during a median follow up of 9.9 years.(27)

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

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

C3G and primary IC-MPGN are diagnosed through kidney biopsy which can show the complement deposits when examined under a microscope. (28) A kidney biopsy is a procedure consisting of removing a small piece of kidney tissue through a special needle for microscopic analysis. While it is an invasive procedure, it is critical for diagnosing these conditions and assessing the extent of kidney damage. The examination is carried out under local anaesthesia or under short general anaesthesia in children. Complications of the procedure are rare. However, they can include bleeding, pain, and development of an abnormal connection between two blood vessels (a fistula). (28)

A blood test will also tell if complement proteins are normal and how well the kidneys are working. It can be difficult to diagnose C3G and IC-MPGN because some clinical features overlap with other kidney diseases. Patients and caregivers frequently have a perception that there are delays in diagnosis, (29) and by the time a correct diagnosis is made, kidney function is often significantly impaired. (11, 30)

2c) Current treatment options:

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

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

Current treatments for C3G and primary IC-MPGN have serious limitations. They primarily provide symptom relief and management of proteinuria (protein in the urine) and do not effectively stop disease progression or prevent irreversible kidney damage, particularly in patients at risk of kidney failure.

Supportive care includes the use of ACE inhibitors/ARBs that are used to lower blood pressure, reduce proteinuria and slow kidney damage. A newer class of drugs called SGLT2 inhibitors, helps protect the kidneys and may be given to some people with C3G or IC-MPGN, although this

treatment isn't yet approved for use in children. (31, 32) Other renoprotective (protective of the kidneys) agents are also used, such as lipid-lowering agents. (33)

For patients at risk of progressive kidney damage, immunosuppressants such as steroids or mycophenolate mofetil (MMF) may be prescribed to help. If this approach proves ineffective, patients with C3G (but not primary IC-MPGN) may be treated with eculizumab, even though it is not approved for this condition. However, a NICE evidence summary (34) acknowledges that patients may not respond to eculizumab therapy, and in the UK it is only used for patients who have recurrent disease following a kidney transplant. (35)

Patients with C3G and primary IC-MPGN often continue to experience worsening kidney function or irreversible damage, resulting in a steady progression to kidney failure. (16, 36) Dialysis and a kidney transplant are options for patients who have kidney failure (12), although disease recurrence occurs in the majority of patients following a kidney transplant. (13)

Figure 1 shows the current treatment pathway and, in light blue boxes, where the new treatment (pegcetacoplan) could be prescribed. Pegcetacoplan can be integrated with current standard of care treatments to preserve kidney function and prevent disease progression.

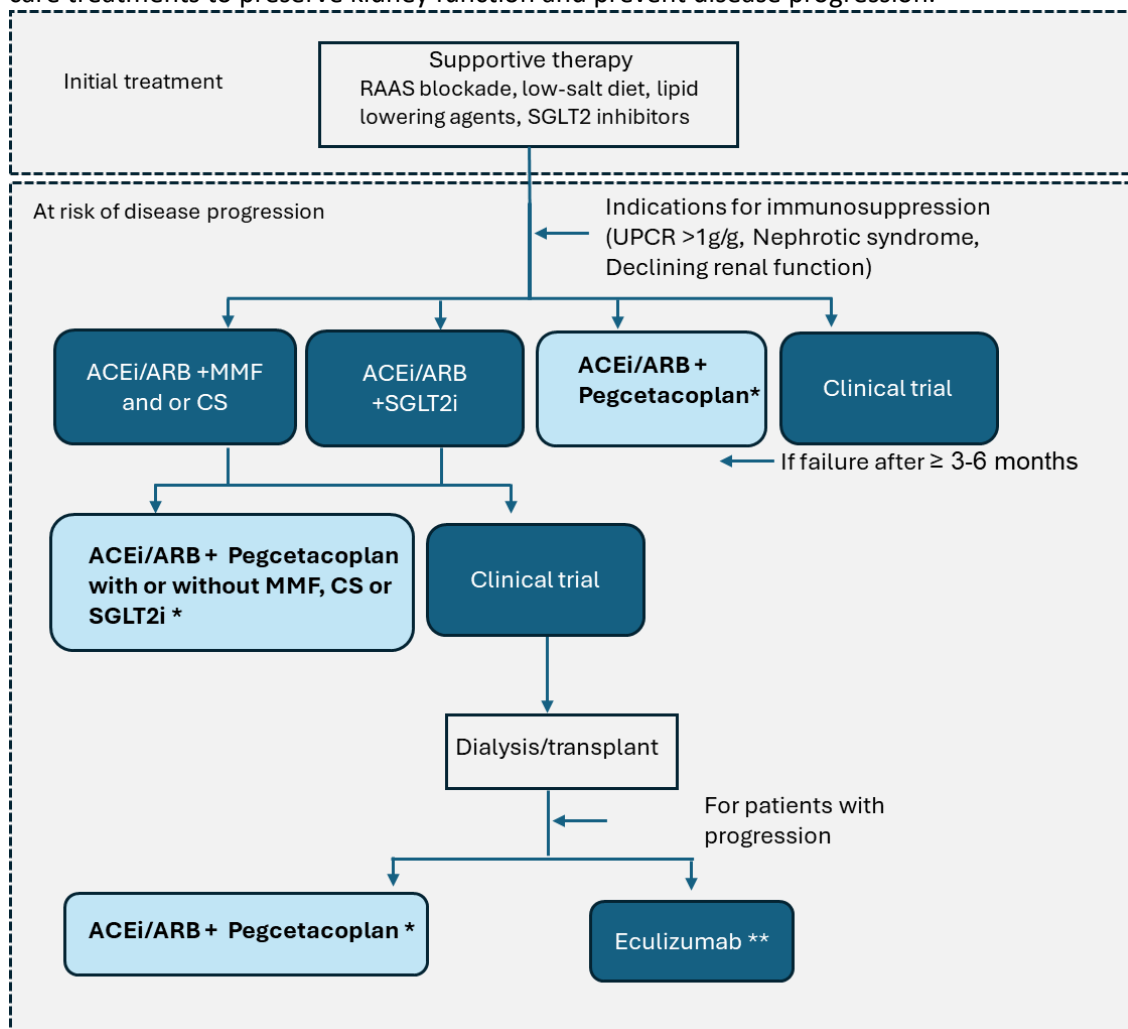


Figure 1. The current treatment pathway is based on KDIGO treatment guidelines (37) shown in dark blue boxes. *Pegcetacoplan is likely to be used alongside an ACE inhibitor or ARB (shown in light blue boxes). ** Eculizumab is used off-label, and in the UK it is only available for patients with C3G who have undergone a kidney transplant.

Abbreviations: MMF - mycophenolate mofetil, UPCR - urine protein/creatinine ratio, RAAS, - renin angiotensin system; SGLT-2, - sodium-glucose co-transporter-2

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

Context:

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

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

The Adelphi Real World C3G/IC-MPGN Disease Specific Programme (DSP)TM is a multinational programme, where data are collected from physicians and patient/caregivers during routine clinical practise. In the current survey, data were collected from France, Germany, Italy, and Spain, the United Kingdom (UK; C3G only), and the US between July 2022 and June 2024. (38) Data collected in this survey that were pertinent to patients, included a patient self-completion form (PSC) capturing the patient perspective, and a caregiver self-completion survey (CSC) capturing the caregiver experience. If the patient was under 18 years, the caregiver completed the PSC on the patient's behalf. The PSC collected responses to validated quality of life (QoL) questionnaires and other data relating to the patient experience and the impact of the condition on their daily lives.

Physicians reported that only 20% of 266 patients with C3G and 23% of 201 patients with primary IC-MPGN were very satisfied with their treatment. Among adults with C3G, the proportion who were very satisfied with treatment was 17%, and 59% among adolescents. For patients who were dissatisfied with treatment, the most common reason was a primary lack of efficacy (initial non-response) in 50% of 22 C3G patients and lack of symptom improvement in 39% of 28 primary IC-MPGN patients.

In another survey of data drawn from the Adelphi DSPTM, (14) patients with C3G were invited to voluntarily complete a survey, self-reporting the impact of fatigue within the last seven days via the Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue and health-related QoL via the EQ-5D-5L, and the EuroQol Visual Analogue Scale (EQ-VAS). The survey also included symptoms experienced at the time of survey and which symptom(s) were the most bothersome at the time of survey. 100 patients completed the survey (EU5 n=29, China n=55, Japan n=5, US n=11). The median age was 41.5 years and 63% were male. Where reported (n=99), patients had been diagnosed with C3G for a median of 1.9 years.

C3G was shown to have a debilitating impact on a patient's quality of life, in particular, due to fatigue (FACIT-fatigue score of 30.3 compared to the mean general population score of 43.5 (39) indicating severe fatigue). Scores were notably lower for patients with CKD stages 4/5, dropping to 27.8; 36.1% worse than the general population. Fatigue was described as the second most distressful symptom (18%). Distress to patients was also caused by foamy urine (20%) and swollen hands/feet/ankles (40% in patients with CKD stages 4/5).

QoL was notably lower for patients with stage 4/5 of CKD. Patient EQ-VAS scores ranged from 46.8 to 66.7, lower than the mean general population score of 78.16 (lower scores indicate poorer QoL). C3G patients also experienced worse EQ-5D utility scores compared to the mean general

population score of 0.84; CKD Stage 1 patients had a mean score of 0.67; Stage 4/5 patients had a lower mean score of 0.58.

The burden of primary IC-MPGN on patients was reported in another survey from the Adelphi DSP™. (40). In this analysis, patients were drawn from France, Germany, Italy, Spain and the US. Nephrologists, paediatric nephrologists, and internal medicine specialists (IMs) completed an online patient record form including data relating to clinical characteristics, patient journey, hospitalisations, patients' quality of life (QOL), and impact on patients' ability to work. These same patients or their parents/caregivers voluntarily completed the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT Fatigue), where scores ranged from 0-52 with higher scores representing better QOL, and the Work Productivity and Activity Impairment questionnaire (WPAI), with higher scores representing greater impairment and less productivity.

In total, patient self-reported data was available for 54 patients (US: 15, EU4: 39). 11% of patients were paediatric (US: 4%, EU4: 15%), with a mean age of 13.4 years (US: 15.0], EU4: 13.2), and 89% were adults (US: 96%, EU4: 85%) with a mean age of 45.7 years (US: 44.7], EU4: 46.3). 57% of patients were male (US: 55%, EU4: 58%), and the mean time since diagnosis was 2.7 years (US: 1.5, EU4: 3.4).

In total, 25% of patients had a caregiver (particularly for patients in Europe, US: 4%, EU4: 37%), with the majority of patients receiving care from a professional caregiver (Total: 57%, US: 67%, EU4: 56%). The majority of physicians reported agreement that patients' primary IC-MPGN was a major problem in everyday life, caused considerable emotional upset, and a considerable impact on ability to work/study.

The most frequent symptoms experienced by patients, as reported by physicians were proteinuria (Total: 56%, US: 73%, EU4: 45%), fatigue (Total: 36%, US: 36%, EU4: 36%), hypertension (Total: 28%, US: 33%, EU4: 26%) and haematuria (Total: 23%, US: 27%, EU4: 21%). Patients reported that their most bothersome symptoms were fatigue (Total: 43%, US: 54%, EU4: 39%), high blood pressure (Total: 20%, US: 54%, EU4: 8%) and sleep problems (Total: 16%, US: 15%, EU4: 17%). The mean FACIT- fatigue score, as reported by patients at the time of data collection was 34.9 (population norm: 43.5). Patients reported that in the seven days prior to data collection they missed on average, 8.6% of work time, impairment whilst working was reported to be 35.6%, overall work impairment was 31.9% and non-work-related activity impairment was 38.5%.

All of these studies show the substantial humanistic burden of C3G and IC-MPGN which remains high despite access to conventional therapy.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Pegcetacoplan is a novel drug that is designed to control C3 overactivation. It acts by binding to the complement protein C3, blocking its activation. This prevents the excessive C3 deposits in the kidneys that results in inflammation and kidney damage.

Unlike existing complement inhibitors, such as eculizumab, which inhibits the complement protein C5, pegcetacoplan offers a more targeted mechanism of action with the potential to prevent kidney damage more effectively in adults and adolescents with C3G and primary IC-MPGN, both pre- and post-transplant.

Across all completed clinical trials in C3G and primary IC-MPGN, pegcetacoplan has demonstrated good tolerability and very few serious side effects. As the treatment works by suppressing part of the immune system, patients need to be vaccinated against certain bacteria to prevent infections.

Pegcetacoplan is approved for use in another condition, Paroxysmal Nocturnal Haemoglobinuria (PNH), and has been submitted for regulatory approval to treat C3G and primary IC-MPGN in the UK.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Pegcetacoplan may be used together with standard of care medications, such as ACE inhibitors (e.g. ramipril, lisinopril) or angiotensin II receptor blockers (ARBs) (e.g. losartan, candesartan). Notably, in the phase 3 trial (VALIANT), similar proportions of patients on pegcetacoplan (98.4%) and placebo (100.0%) were receiving concomitant medications, including ACEi/ARBs and immunosuppressants. Pegcetacoplan was well tolerated, with safety and tolerability comparable with the placebo. Moreover, in a post-hoc analysis of the VALIANT study (41), pegcetacoplan had a similar effect in terms of efficacy (and safety) regardless of whether patients were on immunosuppressants or not.

ACEi/ARBs inhibitors are generally well-tolerated, with adverse events ranging from dry cough (with ACE inhibitors) and dizziness to more severe reactions such as angioedema and hyperkalaemia. (33, 42, 43) These medications work by lowering blood pressure and general kidney protective properties independent on blood pressure reduction.

Immunosuppressants, such as corticosteroids, can cause side effects like weight gain, infections, hypertension, bone loss and mood changes, especially with long-term use. (44) MMF is a drug that helps control the immune system by preventing certain immune cells from growing. It can cause side effects like stomach upset, nausea and headaches. These medications work by suppressing the immune system, but have demonstrated limited effectiveness in treating C3G and primary IC-MPGN as they do not impact the underlying cause of the disease. (33)

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Adults of any weight and adolescents weighing ≥ 50 kg will receive a subcutaneous infusion of 1080 mg (20 mL) twice weekly. For adolescents weighing 35 to < 50 kg, the first dose will be 648 mg (12 mL), the second dose of 810 mg (15 mL), and the maintenance dose is 810 mg (15 mL) and this will be given twice weekly. For those weighing 30 to < 35 kg, the first and second doses are both 540 mg (10 mL) and the maintenance dose is 648 mg (12 mL), twice weekly.

Pegcetacoplan would be prescribed in secondary care (e.g. by a specialist) with routine follow-up in secondary care.

There is no specific data to support stopping treatment. However, in a recent advisory board meeting (Sobi, d.o.f) (45) of clinical experts in the UK, the clinician view was that patients who reached a < 1 g/g UPCR (which is a marker of improvement in disease) might stop treatment based on efficacy. Conversely, if the treatment was not effective, all advisors stated treatment would be stopped.

3d) Current clinical trials

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

Phase 3 – VALIANT study/NCT05067127

VALIANT was a randomised controlled study assessing the efficacy and safety of pegcetacoplan in patients with C3G or primary IC-MPGN aged ≥ 12 years (weighing at least 30kg), native and transplant kidneys. 124 people were enrolled in the study and the study completed on 14/01/2025. This was an international study with 122 study sites across 19 countries, including 9 sites in the UK.

The trial included patients aged at least 18 years, and where approved, adolescents (aged 12-17 years) weighing at least 30kg. All patients had a previous diagnosis of C3G or primary IC-MPGN (with or without previous renal transplant), and evidence of active renal disease.

Participants received pegcetacoplan (N=63) or placebo (N=61) in addition to a stable regimen of concomitant medications, including RAAS inhibitors and immunosuppressants.

For adults taking part in the study, active disease was confirmed by a renal biopsy. Adolescents taking part did not need to provide a biopsy, but evidence of active disease was required, such as levels of the protein C3 from a blood sample.

Key exclusion criteria included previous exposure to pegcetacoplan, evidence of improving renal disease in the 8 weeks prior to screening and C3G or IC-MPGN caused by another condition (e.g. malignancy, infection, an autoimmune disease).

Links to further information on the trial:

- <https://clinicaltrials.gov/study/NCT05067127>
- https://www.sobi.com/sites/sobi/files/Sobi%27s-Aspaveli%C2%AE-and-Phase-3-VALIANT-data-in-Nephrology_0.pdf

Publications from the trial:

The results from VALIANT have been accepted for publication in the *NEJM* (46)

Phase 3 extension – VALE study / [NCT05809531](https://clinicaltrials.gov/study/NCT05809531)

VALE is an ongoing phase 3 extension study of VALIANT to evaluate the long-term efficacy and safety of pegcetacoplan in patients aged 12 and older with C3G and primary IC-MPGN (pre and post-transplant) who completed the VALIANT study through to Week 52, and achieved clinical benefit from receiving pegcetacoplan in the opinion of the investigator.

The patients in VALE continue to receive twice-weekly doses of pegcetacoplan for a minimum of approximately 2.5 years. Approximately 124 people will take part in the trial, which is expected to complete in July 2027. A data cut of the trial was taken on 20th June 2024, at which point, 53 participants from 44 sites were taking part in the study across 15 countries, including 2 sites in the UK.

Links to further information on the trial:

- <https://clinicaltrials.gov/study/NCT05809531>
- https://scielibrary.sobi.com/sites/default/files/documents/Nester_VALE_TiP_ASN2024_Poster.pdf

NOBLE study / [NCT04572854](https://clinicaltrials.gov/study/NCT04572854)

NOBLE is a phase 2 open-label, randomised, controlled multicentre study to assess the efficacy and safety of pegcetacoplan compared with SoC in 13 patients aged 18 and older with biopsy-proven post-transplant recurrence of primary C3G or IC-MPGN. Participants had to have stable (not improving) or worsening disease in the 2 months preceding the first dose of pegcetacoplan. Participants received pegcetacoplan (N=10) or SoC (concomitant medications, including RAAS inhibitors and immunosuppressants; N = 3). The study was conducted at 23 sites across 11 countries. Patients who experienced clinical benefit from pegcetacoplan could participate in Part B of the study; a long-term extension to continue receiving pegcetacoplan until it is commercially available.

Key exclusion criteria included previous exposure to pegcetacoplan, and evidence of rejection on the screening renal biopsy. Results at week 12 of the study are published. (47)

The NOBLE study is not the main source of evidence for pegcetacoplan, but links to further information on the trial are included below:

- <https://clinicaltrials.gov/study/NCT04572854>
- <https://pubmed.ncbi.nlm.nih.gov/39810766/>

DISCOVERY study / [NCT03453619](https://clinicaltrials.gov/study/NCT03453619)

DISCOVERY was a phase 2 single arm, open-label study to assess the efficacy and safety of pegcetacoplan in 21 patients aged 18 and older (16 years of age for C3G) with a diagnosis of immunoglobulin A nephropathy (IgAN), lupus nephritis (LN), primary membranous nephropathy (MN), or C3G (without a history of solid organ transplant; N=8). In the C3G group, participants had to have a confirmed diagnosis of C3G either by kidney biopsy or low C3 blood levels. They also had to have stable or worsening kidney disease while on optimised treatment for ≥2 months before the first dose of pegcetacoplan. Patients with kidney disease secondary to another condition (e.g., infection, malignancy, monoclonal gammopathy, and medication) were excluded. All participants received daily pegcetacoplan.

The study had 17 locations within the US and completed on 26th August 2023. The results from the trial have been published. (48)

The DISCOVERY study is not the main source of evidence for pegcetacoplan, but links to further information on the trial are included below:

- <https://clinicaltrials.gov/study/NCT03453619>
- <https://pmc.ncbi.nlm.nih.gov/articles/PMC10658235/>

3e) Efficacy

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

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

VALIANT is the main trial to evaluate the efficacy of pegcetacoplan in patients with C3G and primary IC-MPGN.

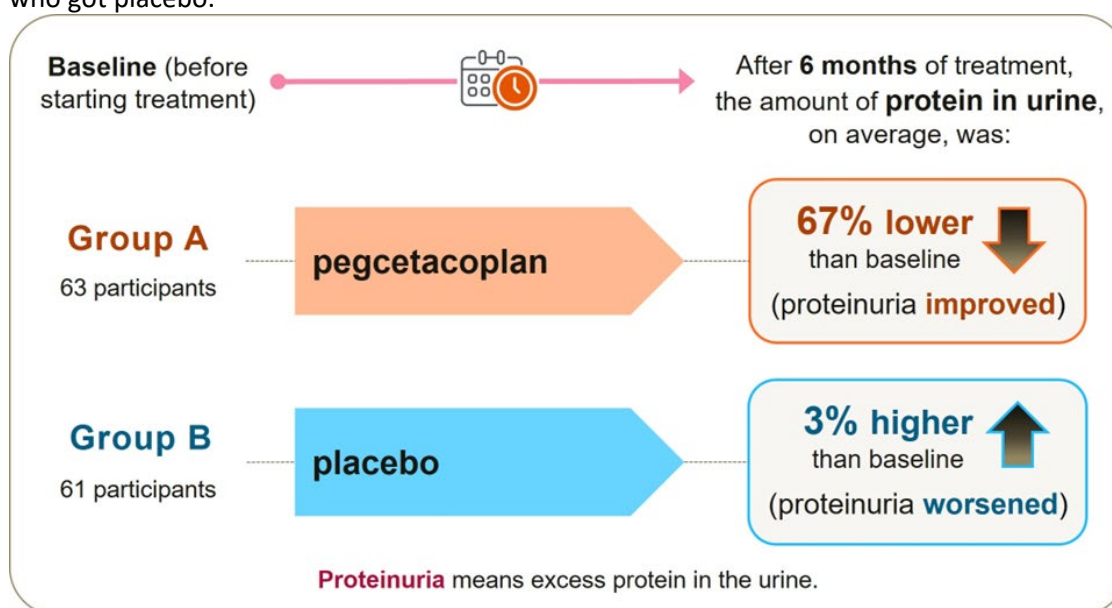
This section presents overall results of 63 participants who got pegcetacoplan (Group A) and 61 participants who got placebo (Group B) in Part 1 of the study.

Researchers had different questions they wanted to answer in the study:

Did pegcetacoplan help to reduce protein in the urine?

Proteinuria is an indicator of kidney damage and is monitored by the urine protein-to-creatinine ratio (UPCR). Researchers checked the amount of protein in the participants' urine at baseline (before starting treatment) and then compared it with the amount of protein in the participants' urine after 6 months of treatment in Part 1.

The figure below shows the results of participants who got pegcetacoplan compared with those who got placebo.



Compared with placebo, pegcetacoplan given for 6 months reduced the amount of protein in the urine. This corresponded with a substantial increase in the proportion of participants with a mild level of proteinuria after 6 months (8% before treatment and 51% after 6 months of treatment), and a marked decrease in the proportion of participants with more severe proteinuria (38% before treatment vs. 14% after 6 months of treatment).

Did pegcetacoplan help to stabilise kidney function?

Estimated glomerular filtration rate (eGFR) is a key indicator of kidney function and helps clinicians assess the presence and severity of kidney disease. Researchers found, after 6 months of treatment with pegcetacoplan, significantly more patients (49%) had a stable or improved eGFR together with a reduction in proteinuria, compared to only 3% of participants in the placebo group. Pegcetacoplan treatment also slowed down the decline in kidney function over 6 months (-1.5) compared to the group receiving placebo (-7.8). This represents a clinically important benefit given that eGFR is a key marker of kidney function and is used to define kidney failure. (49)

Did pegcetacoplan reduce the amount of C3 deposits in the kidney?

Pegcetacoplan is a novel drug that is designed to control C3 overactivation. It acts by binding to the complement protein C3, blocking its activation thus preventing the excessive C3 deposits in the kidneys that results in inflammation and kidney damage. Researchers checked the amount of C3 protein from a kidney biopsy, in adult participants in the trial. They use a technique which stains the tissue with a fluorescence dye or probe which binds to the C3 protein. They found that a greater proportion of participants (74%) had reduced C3 staining after 6 months of treatment with pegcetacoplan compared to 12% of participants in the placebo group. This showed that pegcetacoplan is working by preventing the buildup of C3 complement protein in the kidneys. Consistent with the mechanism of action of pegcetacoplan, the amount of C3 protein in the blood increased.

Participants who switched from placebo to pegcetacoplan (Part 2 of the study) also exhibited notable improvements.

- Of the participants who received pegcetacoplan for 52 weeks, 67% of had a clinically meaningful reduction in proteinuria
- Of the participants who were on placebo for the first 26 weeks and switched to pegcetacoplan for the next 26 weeks, 51% had a clinically meaningful reduction in proteinuria
- Stable eGFR following treatment with pegcetacoplan was maintained throughout the study.

VALE is a source of longer term follow up data for the use of pegcetacoplan

The summary of results presented here are considered interim data as the study is ongoing. Generally, the efficacy results from this long-term extension study demonstrated a sustained treatment effect of pegcetacoplan on reducing levels of protein in the urine and stabilisation of kidney function measured by eGFR in patients with C3G or primary IC-MPGN.

- Pegcetacoplan treatment resulted in sustained, substantial and clinical meaningful proteinuria reduction through to week 64. Of the 53 participants, 71% had a reduction in UPCR at week 64 compared to baseline (before treatment commenced). The proportion of participants who achieved mild proteinuria (<1g/day) was sustained starting at 12 weeks (44.9%) through to week 48 (53.8%).
- eGFR Change Over Time: Pegcetacoplan treatment reduced the rate of decline of eGFR over time. The mean change in eGFR slightly increased through to week 26 (5.9), and then remained relatively unchanged through to week 64 compared to the pretreatment baseline. The proportion of participants with stable or improved eGFR values from pretreatment baseline was sustained starting at week 8 (92%) through to week 64 (81%).

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

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

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

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

In the main trial (VALIANT) QoL was measured using the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale and the Kidney Disease Quality of Life (KDQOL) instrument. The

FACIT assessment measures fatigue levels and their impact on daily life, with higher scores indicating less fatigue.

No meaningful difference was found between pegcetacoplan and placebo in terms of fatigue. This may be because most patients enrolled in VALIANT were in the earliest stages of kidney disease, with a smaller number associated impact on their levels of fatigue. Similarly, no meaningful difference was observed in the KDQOL (Kidney Disease Quality of Life) scores between pegcetacoplan and placebo. Again, this is most likely because most patients had earlier stages of kidney disease in the trial.

Patient reported outcomes were not assessed in the supporting phase 2 studies and VALE is ongoing and has yet to report data on these outcomes due to small patient numbers.

3g) Safety of the medicine and side effects

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

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

Pegcetacoplan has demonstrated an acceptable safety profile, with good tolerability and no serious treatment-emergent adverse events (TEAEs, meaning side effects that occur after use of the studied drug) leading to discontinuation or death in either the phase II or III trials. Pegcetacoplan was well tolerated in key subgroups of age (adolescents and adults) and transplant status (non-transplant or post-transplant). No trends were observed leading to treatment withdrawal or study discontinuation, and no rejection episodes or graft loss were reported in post-transplant recipients.

The overall results of 120 participants who got at least one dose of pegcetacoplan in the VALIANT study are presented here. 63 participants started pegcetacoplan in Part 1 and 57 participants who got placebo in Part 1 then started pegcetacoplan in Part 2.

49 out of 120 participants (41%) who got pegcetacoplan had side effects in the study. Overall, 3 participants stopped pegcetacoplan treatment because of a side effect.

The most common side effects were infusion site reactions (28.6% [pegcetacoplan] vs 27.9% [placebo]), pyrexia (fever) (19.0% [pegcetacoplan] vs 9.8% [placebo]), nasopharyngitis (common cold) (17.5% [pegcetacoplan] vs 11.5% [placebo]), headache (12.7% [pegcetacoplan] vs 16.4% [placebo]), and vomiting (7.9% [pegcetacoplan] vs 13.1% [placebo]). The majority of side effects were mild or moderate in severity.

In total, 21 (33.3%) participants in the pegcetacoplan group and 16 (26.2%) participants in the placebo group had an infusion-related side effect (e.g. injection site swelling (3.2% [pegcetacoplan] vs 9.8% [placebo]) and injection site pain (3.2% [pegcetacoplan] vs 8.2% [placebo])).

One participant in the pegcetacoplan group had a serious side effect (fever) that was considered by the investigator to be related to the study drug; no other serious side effects were reported.

Interim analysis from VALE demonstrates that pegcetacoplan is well tolerated with continued treatment. The most commonly reported side effect since receiving the first dose of pegcetacoplan were fever (16 [13.3%]), nasopharyngitis (common cold (15 [12.5%]), diarrhoea (11 [9.2%]) and headache (11 [9.2%]) and there has not been increased reporting of these side effects in this extension study, and no pyrexia nor headache side effect was reported in this long-term extension study.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

Pegcetacoplan is the first available treatment to directly target C3 overactivation, which is a key underlying factor in the disease. The goal of treatment in C3G and primary IC-MPGN is not just to reduce inflammation but to stop disease progression. Pegcetacoplan offers the most comprehensive blockade of the complement cascade, which is necessary to prevent both inflammation and structural damage to the kidneys.

Existing supportive therapies do not address the cause of the disease and are ineffective at preventing disease progression. Patients with C3G and primary IC-MPGN are likely to be faced with worsening kidney function and progression to kidney failure requiring dialysis and/or transplantation, diminishing their quality of life, and increasing the risk of mortality.

In the VALIANT trial pegcetacoplan showed a favourable treatment effect on proteinuria, eGFR and C3 deposits in the kidney, all of which are outcomes that provide convincing evidence of the benefits of the treatment in C3G and primary IC-MPGN and are believed to be good signals of overall kidney health. The treatment effect was consistent across all patient populations in the trial e.g. adolescent, adult, native and post-transplant populations.

The safety profile of pegcetacoplan in patients with C3G and primary IC-MPGN is favourable and consistent with the known safety profile for pegcetacoplan in the other condition it is used for, paroxysmal nocturnal haemoglobinuria (PNH). This is supported by a very low number of patients who stopped treatment with pegcetacoplan (<2%) in the VALIANT trial, and in the previous NOBLE phase 2 study in which there were no patients who stopped the treatment.

Pegcetacoplan provides a convenient twice-weekly dosing for patients. It is administered subcutaneously using a commercially available syringe infusion pump, which can be self-administered at home.

Pegcetacoplan is expected to improve the quality of life for patients and caregivers by positively impacting emotional, physical and social wellbeing. These improvements are likely to translate into reduced caregiver burden and improved productivity for patients.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

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

Response:

There are some potential disadvantages for patients treated with pegcetacoplan:

- Injection site reactions
- Patients may need support with injections, especially for adolescents.
- Patients are required to be vaccinated against encapsulated bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*) and should be closely monitored.
- Pegcetacoplan is not recommended during pregnancy or breastfeeding.

3i) Value and economic considerations

Introduction for patients:

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

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

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

How the model reflects the condition:

- The structure of the model compares treatment with pegcetacoplan versus standard of care treatments alone and iptacoplan for treating adolescent and adult patients with C3G or primary IC-MPGN. UPCR is a key predictor of disease progression and was used in the model to reflect disease severity and progression, together with eGFR levels, over time. Specifically, the rate of eGFR decline, and thus progression through stages of CKD is dictated by UPCR levels, with higher levels of UPCR associated with more rapid kidney function deterioration. As the disease progresses, continued eGFR decline can result in ESKD, necessitating costly dialysis or kidney transplant procedures that negatively impact patient quality of life.

Modelling how much a treatment extends life:

- Results from the VALIANT trial showed that pegcetacoplan impacts disease progression by reducing C3c staining on kidney biopsies indicating suppression of complement-mediated injury in the kidneys. This effect translates into reductions in UPCR levels, thereby slowing the decline in eGFR and delaying disease progression. By delaying disease progression,

patients avoid the higher risk of death associated with later CKD stages, ESRD, dialysis and transplants. Therefore, pegcetacoplan is expected to provide life extending benefits.

- The VALIANT trial data was used in the economic model and informs the probability that patients in the model experience certain outcomes such as reduction in UPCR and stabilisation of eGFR. 26-week placebo data and 52-week pegcetacoplan data from the VALIANT trial were used to inform the base case model results.

Modelling how much a treatment improves quality of life

- Improvements in quality of life are identified in the model from improvements in disease progression whereby patients spend more time in earlier chronic kidney disease (CKD) stages where quality of life is expected to be higher. Additionally, pegcetacoplan reduces the need for some patients to undergo dialysis which has been identified in the literature as having a significant impact on a patient's quality of life.
- Quality of life was captured in the VALIANT trial using the EQ-5D questionnaire. These responses were converted to 'utility' values, which measure quality of life on a scale from 0 (death) to 1 (perfect health). Known disease specific utility values from the literature ((50)) for CKD stages 3-5 for patients were also used due to limited sample size in VALIANT, whereas VALIANT EQ-5D data was used for patients in CKD stages 1-2. Patients undergoing dialysis are expected to observe worse HRQoL than those without ESKD. Dialysis associated utility values were captured from the literature. (51)

Modelling how the costs of treatment differ with the new treatment

- Pegcetacoplan is administered twice weekly as a 1,080mg subcutaneous infusion with a commercially available syringe system infusion pump that can deliver doses up to 20 mL. Pegcetacoplan is assumed to be self-administered subcutaneously by all patients. This reduces the need for administration by clinical staff and its associated costs.

Uncertainty

- The quality of life impact of undergoing kidney transplantation was assumed to be equal to the lowest utility identified in the literature (i.e. patients undergoing haemodialysis) since no specific utility values were identified in the literature.
- Another assumption made in the model included patients achieving UPCR levels < 1g/g (stable disease) pausing treatment until relapse. This was supported by clinical expert opinion.
- Patients are assumed to adhere 100% to their treatment dosing. This assumption ensured the acquisition costs captured in the model aligned with the clinical outcomes from the VALIANT trial due to the high adherence observed in the trial.
- Deterministic sensitivity analysis was conducted to assess the sensitivity of individual parameters and their impact on the model results. This analysis identified that transitions into and out of the stable disease health state were the most influential parameters on the model outcomes.
- Additionally, probabilistic sensitivity analysis was conducted which simultaneously varied all eligible parameters in the model to assess the combined uncertainty in the model across all parameters. Scenario analyses were also performed on key model assumptions, including data source choices. Of the eight scenarios explored, the scenario in which 6-month data from VALIANT was used in both treatment arms had the greatest effect on the model outcomes.

- External validation against other published economic evaluations was not feasible, as no existing cost-effectiveness models were identified for any treatment within IC-MPGN or C3G.

Additional factors

- Pegcetacoplan is not expected to meet the criteria for a severity modifier.
- Caregiver burden: C3G and IC-MPGN frequently present earlier in life than many other chronic kidney diseases, with diagnoses reported in childhood and adolescence. Early onset has important implications, as the conditions can disrupt education, limit long-term career development, and increase lifetime productivity losses, none of which are captured within the QALY framework. Furthermore, early disease onset places a significant burden on caregivers, particularly parents of adolescent patients, who are responsible for managing treatment, coordinating medical care, and supporting psychosocial wellbeing over many years. These caregiver responsibilities and broader societal impacts are not reflected in the modelled health outcomes but represent meaningful benefits of effective treatment.
- Paediatric patients: Feedback from paediatric nephrologists indicated that paediatric patients typically require additional healthcare resources. In particular, those with CKD stage 4–5 would receive psychology, play therapy, and dietitian input. To avoid additional complexity, the current model does not differentiate health-state unit costs or resource use between paediatric and adult patients. As a result, potential cost savings from improved outcomes in paediatric patients are not explicitly captured and therefore represent an additional potential saving from treatment with pegcetacoplan not reflected in the model.
- Kidney failure risk of death assumption: Evidence from the literature suggests that there is an increased risk of death in the first 3–6 months following kidney failure. Despite this, the current model for pegcetacoplan adopts a conservative assumption that the risk of death among individuals with kidney failure remains constant over time. This approach was taken to maintain simplicity and transparency in the model and to avoid the additional complexity that would arise from introducing tunnel states. As a result, potential QALY gains from reducing early mortality following kidney failure are not captured within the current model.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Pegcetacoplan is the first disease-modifying treatment for adolescents with primary C3G and all patients with primary IC-MPGN, that can be used with current standard of care options to effectively target C3 complement dysregulation; a key driver of inflammation and kidney damage that leads to rapid progression to kidney failure.

By specifically targeting C3 it prevents further C3 fragment deposition in the glomeruli (a small network of blood vessels) of the kidney thus addressing the primary cause of C3G and primary IC-MPGN.

Unlike existing complement inhibitors such as eculizumab, which inhibits the complement protein, C5, pegcetacoplan offers a more targeted mechanism of action with the potential to prevent kidney damage more effectively in adults and adolescents with C3G and primary IC-MPGN, both pre- and post-transplant.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues [here](#)

The company asked NICE to consider whether the longer waiting times for kidney transplants faced by Black and Asian people represents a health inequality.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Further information on treatment guidelines:

- KDIGO guidelines for glomerular diseases <https://kdigo.org/guidelines/gd/>
- NICE guidelines CKD <https://www.nice.org.uk/guidance/ng203>
- NICE evidence summary C3G (post-transplant): eculizumab
<https://www.nice.org.uk/advice/esuom44/chapter/Key-points-from-the-evidence>
- NICE evidence summary C3G in the native kidney: eculizumab
<https://www.nice.org.uk/advice/esuom49/chapter/full-evidence-summary>
- NICE: chronic kidney disease; assessment and management
<https://www.nice.org.uk/guidance/ng203>

Kidney Associations & Registries:

- RaDaR (National Registry of Rare Kidney Disease) <https://www.ukkidney.org/rare-renal>
- UK Kidney Association <https://www.ukkidney.org/>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>

- EFPIA – Working together with patient groups:
<https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe:
http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Complement system a central component of the immune system involved in the defence against pathogens. Helps remove pathogens from the body.

Eculizumab is an antibody that blocks the complement protein C5. It has no effect on C3 levels

Estimated glomerular filtrations rate (eGFR) is used to evaluate the pace of filtration in the kidneys

Immunosuppressants target inflammation in the glomerular of the kidney and is often indicated for patients with worsening kidney function

Lipodystrophy is the abnormal distribution of fat in certain areas of the body

Proteinuria is the elevated presence of proteins in the urine. It is used as a marker of kidney damage.

Renin-angiotensin-aldosterone system (RAAS) inhibitors are a group of drugs that act by inhibiting the renin-angiotensin-aldosterone system (RAAS) and include angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin-receptor blockers (ARBs). They have a demonstrated clinical benefit in a variety of conditions including hypertension and cardiovascular disease

UPCR urine protein-to-creatinine ratio test helps assess kidney function by measuring the amount of protein and creatinine in a urine sample. It is used to detect and monitor kidney disease or damage, especially in cases where protein is present in the urine.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Clarification questions

September 2025

File name	Version	Contains confidential information	Date
ID6489 Pegcetacoplan clarification response [CON]	1.0	Yes	13th October 2025
ID6489 Pegcetacoplan clarification response [CON]	2.0	Yes	16th October 2025

Notes for company

Highlighting in the template

Square brackets and [REDACTED] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [REDACTED] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press **DELETE**.

Section A: Clarification on effectiveness data

Literature searches

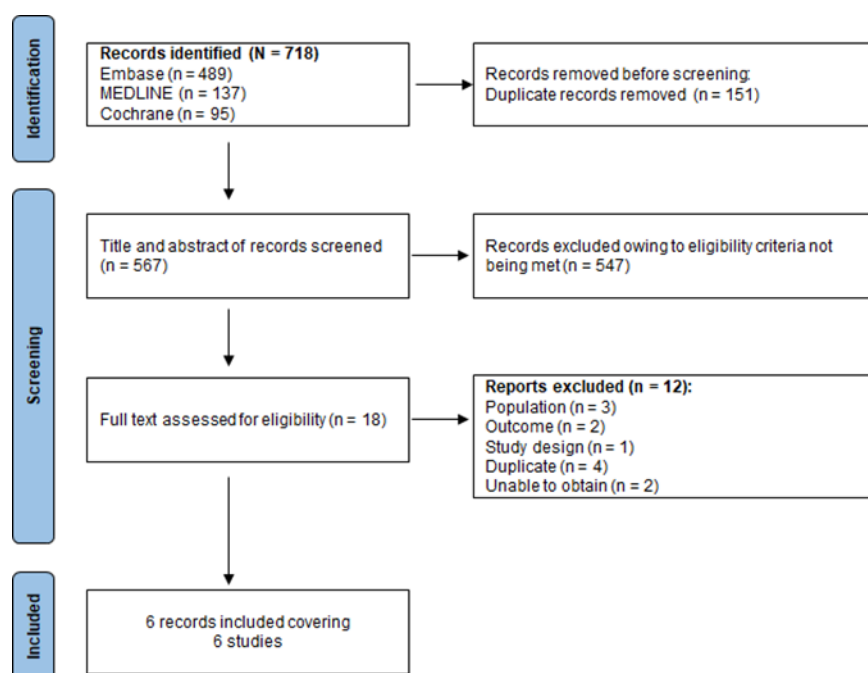
A 1. Priority question: The list of comparators included in the clinical effectiveness search strategies (Appendix B; Tables 103-108) does not appear to reflect all the comparators in the decision problem table (Table 1 in the company submission [CS]). Please explain why searches have not been conducted for all comparators, particularly as Section 2.2 of the CS states that 'Due to the rare nature of the disease, the systematic literature review (SLR) was designed to capture trials assessing any intervention for these patients'.

Thank you for your question. At the time the original SLR was originally conducted, the comparators focused on treatments targeting the complement cascade, in particular C3 modulators which were developed for patients with C3G and IC-MPGN. At the time of the search, iptacopan in particular was considered the main comparator. To address this clarification question, and identify any additional studies, an additional search was undertaken (in Embase, MEDLINE and Cochrane on 9 October 2025) which included terms for the original intervention and comparators of interest (pegcetacoplan, iptacopan, ARO-C3, SAR443809, BCX10013, ADX-097, KP104, NM8074 or zaltenibart) as well as terms for standard-

of-care treatments as listed in the decision problem table (angiotensin converting enzyme inhibitors, angiotensin II receptor agonists, corticosteroids, mycophenolate mofetil and sodium-glucose co-transporter-2 inhibitors, other immunomodulatory treatments, eculizumab, etc.). Due to time constraints, the searches focused on randomised controlled trials (RCTs) which provide the most robust evidence for any treatment.

A PRISMA flow diagram for the searches can be found in Figure 1. Briefly, the searches resulted in 718 records and after deduplication, the titles and abstracts of 567 articles were screened by a single reviewer for relevance. Eighteen articles were reviewed at full text and 5 articles, reporting on 6 RCTs, were deemed relevant for inclusion. The 6 RCTs are APPEAR-C3G, (1) ACCOLADE, (2) study 204, (3) Cattran 1985 RCT, (4), the International Study of Kidney Disease in Children, (5) and Giri 2002 RCT. (6) The list of excluded studies and articles included for full text screening are available for review. (7)

Figure 1. PRISMA flow diagram for additional comparators



APPEAR-C3G (NCT04817618) is a phase 3 RCT that is already included in the previous SLR across four congress abstracts; however, a peer-reviewed manuscript has been identified since the last searches (1). The manuscript presents full details of the efficacy and safety outcomes for adult patients with complement 3

glomerulopathy (C3G) receiving iptacopan or placebo over the 6-month, double-blind period and an additional 6-month, open-label extension (OLE) period, and includes patient reported outcomes and additional exploratory analyses. Overall, a statistically significant and clinically meaningful proteinuria reduction at 6 months, along with stabilization of estimated glomerular filtration rate (eGFR) and reduction in C3 deposits was observed with iptacopan compared with placebo. Iptacopan was also shown to have a fast and sustained effect on downregulating the alternative complement pathway and was well tolerated with a favourable safety profile.

A summary of the study details and patient characteristics of the RCTs for avacopan (ACCOLADE, NCT03301467, (2)), danicopan (study 204, NCT03369236, (3)), cyclophosphamide, coumadin and dipyridamole (4), prednisone (5), and nifedipine or enalapril (6) can be found in Table 1.

Table 1. Study details and patient characteristics

	ACCOLADE (NCT03301467)	Study 204 (NCT03369236)^c	Cattran 1985	The International Study of Kidney Disease in Children (Tarshish 1992)	Giri 2002
Study detail					
Country	USA, Canada, Denmark, France, Germany, Ireland, Italy, Spain and the UK	USA and the UK	Canada	-	India
Study design	Phase 2 randomized, double-blind, placebo-controlled trial	Phase 2 double-blind, placebo-controlled study and OLE	RCT	RCT	RCT
Follow-up duration	26 weeks (double-blinded followed by 26-week OLE)	6 months (double-blinded) followed by 6 months OLE	18 months	Up to 5 years	9 months
Intervention/ comparator	Avacopan vs placebo	Danicopan vs placebo	Cyclophosphamide, coumadin and dipyridamole (hereby referred to as treatment) vs control (no specific therapy)	Prednisone vs placebo (lactose)	Nifedipine vs enalapril vs control

	ACCOLADE (NCT03301467)	Study 204 (NCT03369236)^c	Cattran 1985	The International Study of Kidney Disease in Children (Tarshish 1992)	Giri 2002
Dosing	30 mg twice daily	100 mg thrice daily for the first 2 weeks and 200 mg thrice daily thereafter	Cyclophosphamide - 1.5–2.0 mg/kg Coumadin - single daily dose adjusted to maintain the one step prothrombin 2 to 2.5 x control value Dipyridamole - started at 25 mg 4 x daily and increased by 100 mg/24 hr weekly, until full dose of 100 mg 4 x daily reached	40 mg/m ² , every other day for 5 years, given in a single dose in the morning, with a maximum dosage of 60 mg	Nifedipine – 10 mg thrice daily Enalapril – 10 mg daily
Patient characteristics					
Disease	C3G	C3G	MPGN I and II	MPGN I, II and III	Primary MPGN
Native or recurrent^a	Native and recurrent	Native	-	-	-
Patient number	Avacopan, 29 Elevated C5b-9, 20 Normal C5b-9, 7 Placebo, 27 Elevated C5b-9, 22 Normal C5b-9, 7	Danicopan, 6 Placebo, 7	Treatment, 27 Control, 32	Prednisone, 47 MPGN I, 24 MPGN II, 9 MPGN III, 9 Undefined, 5 Placebo, 33 MPGN I, 18 MPGN II, 5 MPGN III, 8 Undefined, 2	Nifedipine, 10 Enalapril, 10 Control, 10
Children, adolescents or adults^a	Adolescents and adults	Adolescents and adults (≥17 years)	-	Children	Adolescents and adults (15–65 years)
Age, years	Mean (SD) Avacopan, 32 (15) Placebo, 37 (18)	Mean (SD) Danicopan, 25.5 (10.5) Placebo, 24.9 (4.9)	Mean (range) Treatment MPGN I, 38 (12–77) MPGN II, 19.7 (6–28) Control MPGN I, 34 (6–70) MPGN II, 19 (7–58)	Mean (SEM) Prednisone, 10.8 (0.36) Placebo, 11.1 (0.50)	Mean (SD; n = 28), 32.0 (10.5)
Male, n (%)	Avacopan, 18 (67.0%) Placebo, 16 (55.0%)	Danicopan, 4 (66.7%) Placebo, 5 (71.4%)	Treatment, 11 Control, 19	Prednisone, 24 (51.1%) Placebo, 19 (57.6%)	-
Time since diagnosis	Mean (SD) duration of C3G, months Avacopan, 50 (46)	Mean (SD) disease duration, years Danicopan, 5.4 (3.0)	-	Mean (SEM) duration of disease, months	-

	ACCOLADE (NCT03301467)	Study 204 (NCT03369236)^c	Cattran 1985	The International Study of Kidney Disease in Children (Tarshish 1992)	Giri 2002
	Placebo, 47 (44)	Placebo, 7.4 (2.3)		Prednisone, 8.9 (1.3) Placebo, 18.1(3.9)	

^aRecurrent disease is defined as C3G/IC-MPGN after kidney transplant and native disease is defined as C3G/IC-MPGN that is not recurrent. ^bAs determined by the inclusion criteria of the trial.

^cPublication for study 204 also contains results from the phase 2 single-arm trial for danicopan which has not been extracted owing to the inclusion criteria being RCTs. C3G, complement 3 glomerulopathy; MPGN, membranoproliferative glomerulonephritis; OLE, open-label extension; RCT, randomized controlled trial; SEM, standard error of the mean; SD, standard deviation

In the ACCOLADE study of avacopan, the primary analysis of the primary efficacy endpoint of change from baseline to week 26 in disease activity in patients with elevated C5b-9 (C5b-9 >244ng/ml) was not statistically significant: there was no significant difference in the least squares (LS) mean difference in change from baseline between patients treated with avacopan and those treated with placebo (−0.0 [95% CI −1.9 to 1.8]; (2)) A secondary analysis of the primary endpoint in the combined C5b-9 strata (those with C5b-9 >244ng/ml and C5b-9 ≤ 244ng/ml) showed no difference between avacopan and placebo (0.1 [−1.4 to 1.7]). The secondary measures of efficacy, including C3G Histological Index for disease chronicity, urine protein-to-creatinine ratio, and eGFR were not different between treatment groups. The overall incidence and type of adverse events for both treatment groups were comparable. No deaths were reported during the study, and no new safety signals were detected. To summarise, the primary endpoint for the study was not met (2)

In study 204 for danicopan, efficacy was assessed with two co-primary endpoints: 1) composite biopsy score changes which incorporated changes in the activity index, glomerular C3c staining, and glomerular macrophage infiltration and a chronicity index and 2) the proportion of patients with a 30% reduction in proteinuria relative to baseline (Nester 2022). The mean change in biopsy scores marginally improved from baseline to week 28 in the danicopan-treated group (n = 5; −2.0) but not in the placebo group (n = 6; 1.3). Proteinuria improvement was not achieved in any of the patients treated with danicopan but was achieved in 1 (20.0%) patient treated with

placebo. Key secondary endpoints included eGFR changes from baseline and proteinuria changes from baseline. No significant increase in eGFR or improvement in proteinuria was observed over time with danicopan nor placebo. In terms of safety, many patients (n = 10 [76.9%]) had at least one treatment-emergent adverse event (AE) during the 6-month blinded treatment period, with most AEs not related to study treatment, of grade 1 severity, and with similar incidences between placebo and danicopan treatment groups. No severe AEs (SAEs) were reported during the 6-month blinded treatment period. One SAE (acute kidney injury) leading to study withdrawal occurred in a patient in the placebo-to-danicopan crossover group during the OLE period. No deaths were recorded during the study period. Overall, this study demonstrated the lack of efficacy of danicopan in patients with C3G (3).

Three of the included RCTs were published and conducted before the re-classification of C3G and IC-MPGN, the outcomes of which are summarised below.

In the Cattran RCT of cyclophosphamide, coumadin and dipyridamole (referred to as treatment) compared with control (no specific treatment), the change in renal function, as measured by both the slope of corrected creatinine clearance and the plasma creatinine reciprocal at 6, 12, and 18 months was not significantly different between treatment and control groups in either patients with membranoproliferative glomerulonephritis (MPGN) type I or II (4). Proteinuria in the treatment and control group was not different at any time point in either patients with MPGN I or II. Side effects of treatment were considerable, resulting in 22% of the treatment group (6/27) being unable to complete the study. This RCT demonstrated that the combination of cyclophosphamide, coumadin and dipyridamole did not provide a significant clinical benefit to patients with MPGN.

In the International Study of Kidney Disease in Children (5) RCT of alternate day prednisone or placebo over a mean period of 41 months, the proportion of patients with treatment failure (primary endpoint), defined as an increase from baseline in serum creatinine of either $\geq 30\%$ or $>35 \mu\text{mol/L}$ (0.4 mg/dl), was non-significant with prednisone vs placebo (36.4% vs 54.5%; $p = 0.087$ one-tailed and $p = 0.164$ two-tailed Fisher's exact). A life-table analysis showed a renal survival rate at 130 months of 61% among patients receiving prednisone and 12% among patients receiving placebo ($p = 0.07$). Of the patients with MPGN I or III, a significantly

smaller proportion of patients had treatment failures with prednisone vs placebo (29.0% vs 57.7%; $p = 0.028$ one-tailed and $p = 0.035$ two-tailed Fisher's exact). Of the patients with MPGN II, treatment failure was similar between prednisone and placebo (55.6% vs 60.0%; $p = 0.657$ one-tailed and $p = 1.0$ two-tailed Fisher's exact). Resolution of both haematuria and proteinuria occurred in 3 patients receiving prednisone and 3 patients receiving placebo. In total, 6 patients died, 2 receiving prednisone and 4 receiving placebo. Despite the primary endpoint not being met, the authors concluded that long-term treatment with prednisone appeared to improve outcomes in children with MPGN, despite the small number of patients and differences in effectiveness between the MPGN types.

In the Giri 2002 RCT (6) of enalapril (angiotensin-converting enzyme inhibitor), nifedipine (calcium channel blocker) or control, enalapril provided protection against progression of renal insufficiency over the 9-month period compared with baseline as observed by a significant decrease in serum creatinine ($p < 0.001$), blood urea and 24-hour albuminuria ($p < 0.001$) and a significant increase in creatinine clearance ($p < 0.001$). Patients treated with nifedipine did not have significant changes in serum creatine levels, blood urea, or creatinine clearance compared with baseline, however, a significant increase in 24-hour albuminuria ($p < 0.001$) was observed. In the control group, serum creatinine and 24-hour albuminuria significantly increased ($p < 0.001$ for both), blood urea increased, and creatinine clearance significantly decreased ($p < 0.001$) from baseline. None of the patients were observed to have side effects leading to withdrawal of the treatments, and no adverse drug reactions were noted. The authors concluded that enalapril provided protection against progression of renal insufficiency in patients with primary MPGN.

In summary, 5 RCTs were identified of comparators that were not included in the original submission. The treatments identified include avacopan and danicopan, both of which did not demonstrate efficacy in patients with C3G. Similarly, in older RCTs of patients with MPGN, combination treatment of cyclophosphamide, coumadin and dipyridamole, and treatment with prednisone, did not meet primary efficacy endpoints demonstrating a lack of significant clinical benefit of these treatments for patients with MPGN. Enalapril demonstrated a protective benefit at slowing renal decline in patients with MPGN, however, the study contained a small number of

patients (n = 28 completed the study across the 3 treatment groups) and should be interpreted with caution.

Searches performed on 9 October 2025 are listed below: :

Embase: <1974 to 2025 October 08>.

#	Searches	Embase
1	membranoproliferative glomerulonephritis/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	23312
2	pegcetacoplan/ or iptacopan/ or (pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LNP023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart OMS-906 or OMS906).mp.	1213
3	(immunosuppress* or IST or steroid* or corticosteroid* or glucocorticoid* or cyclophosphamide or methylprednisolone or tacrolimus or mizoribine or azathioprine or AZA or mycophenolate mofetil or MMF or prednisolone or prednisone or rituximab or eculizumab or complement inhibitor* or danicopan or venircopan or avacopan or angiotensin converting enzyme inhibitor* or ACE inhibitor* or captopril or fosinopril or quinapril or trandolapril or moexipril or enalapril or lisinopril or perindopril or ramipril or benazepril or enalaprilat or angiotensin II receptor antagonist* or angiotensin receptor blocker* or ARB or losartan or valsartan or candesartan or azilsartan or irbesartan or olmesartan or telmisartan or eprosartan or sodium-glucose co-transporter-2 inhibitor* or sodium glucose cotransporter 2 inhibitor* or SGLT2 inhibitor* or dapagliflozin or empagliflozin or canagliflozin or ertugliflozin or immunomodulator* or immunomodulatory treatment* or immunomodulatory therap*).ti,ab.	1420911
4	2 or 3	1421575
5	1 and 4	3630
6	Clinical Trial/ or Randomized Controlled Trial/ or controlled clinical trial/ or multicenter study/ or Phase 1 clinical trial/ or Phase 2 clinical trial/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or exp RANDOMIZATION/ or Single Blind Procedure/ or Double Blind Procedure/ or Crossover Procedure/ or PLACEBO/ or Prospective Study/	3638952
7	(randomi?ed controlled trial\$ or rct or (random\$ adj2 allocat\$) or single blind\$ or double blind\$ or ((treble or triple) adj blind\$) or placebo\$).tw.	1101777
8	((phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*)) or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*))).ti,ab,hw,kf.	1250934
9	or/6-8	4159294
10	5 and 9	516
11	(animal\$ not human\$).sh,hw.	5177234
12	10 not 11	512
13	case study/ or letter/ or case report.tw.	2037821
14	12 not 13	486

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to October 08, 2025>.

#	Searches	Medline
1	Glomerulonephritis, Membranoproliferative/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex	13956

#	Searches	Medline
	mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	
2	(pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LNP023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart OMS-906 or OMS906).mp.	337
3	(immunosuppress* or IST or steroid* or corticosteroid* or glucocorticoid* or cyclophosphamide or methylprednisolone or tacrolimus or mizoribine or azathioprine or AZA or mycophenolate mofetil or MMF or prednisolone or prednisone or rituximab or eculizumab or complement inhibitor* or danicopan or venircopan or avacopan or angiotensin converting enzyme inhibitor* or ACE inhibitor* or captopril or fosinopril or quinapril or trandolapril or moexipril or enalapril or lisinopril or perindopril or ramipril or benazepril or enalaprilat or angiotensin II receptor antagonist* or angiotensin receptor blocker* or ARB or losartan or valsartan or candesartan or azilsartan or irbesartan or olmesartan or telmisartan or eprosartan or sodium-glucose co-transporter-2 inhibitor* or sodium glucose cotransporter 2 inhibitor* or SGLT2 inhibitor* or dapagliflozin or empagliflozin or canagliflozin or ertugliflozin or immunomodulator* or immunomodulatory treatment* or immunomodulatory therap*).ti,ab.	946658
4	2 or 3	946828
5	1 and 4	1699
6	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or PLACEBOS/	1414245
7	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	1266103
8	((clinical adj trial\$) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)) or placebo\$ or randomly allocated or (allocated adj2 random\$)).tw.	893064
9	((phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*)) or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*))).ti,ab,hw,kf.	717538
10	or/6-9	2237320
11	5 and 10	152
12	(animal\$ not human\$).sh,hw.	5337092
13	11 not 12	146
14	case study/ or letter/ or case report.tw.	3653103
15	13 not 14	137

Cochrane: EBMR DARE. NHS Economic Evaluation Database. Health Technology Assessment. Cochrane Methodology Register. EBM Reviews - ACP Journal Club <1991 to September 2025>. EBM Reviews - Cochrane Central Register of Controlled Trials <September 2025>. EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 8, 2025>.

#	Searches	Cochrane
1	Glomerulonephritis, Membranoproliferative/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	994

#	Searches	Cochrane
2	(pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LNP023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart OMS-906 or OMS906).mp.	310
3	(immunosuppress* or IST or steroid* or corticosteroid* or glucocorticoid* or cyclophosphamide or methylprednisolone or tacrolimus or mizoribine or azathioprine or AZA or mycophenolate mofetil or MMF or prednisolone or prednisone or rituximab or eculizumab or complement inhibitor* or danicopan or venircopan or avacopan or angiotensin converting enzyme inhibitor* or ACE inhibitor* or captopril or fosinopril or quinapril or trandolapril or moexipril or enalapril or lisinopril or perindopril or ramipril or benazepril or enalaprilat or angiotensin II receptor antagonist* or angiotensin receptor blocker* or ARB or losartan or valsartan or candesartan or azilsartan or irbesartan or olmesartan or telmisartan or eprosartan or sodium-glucose co-transporter-2 inhibitor* or sodium glucose cotransporter 2 inhibitor* or SGLT2 inhibitor* or dapagliflozin or empagliflozin or canagliflozin or ertugliflozin or immunomodulator* or immunomodulatory treatment* or immunomodulatory therap*).ti,ab.	127218
4	2 or 3	127380
5	1 and 4	154
6	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or PLACEBOS/	288962
7	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	0
8	((clinical adj trial\$) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)) or placebo\$ or randomly allocated or (allocated adj2 random\$)).tw.	769085
9	((phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*)) or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*))).ti,ab,hw,kf.	390025
10	or/6-9	1033923
11	5 and 10	97
12	(animal\$ not human\$).sh,hw.	1252
13	11 not 12	97
14	case report.tw.	3346
15	13 not 14	95

A 2. Priority question: The Medline and Cochrane Library searches use the Emtree controlled vocabulary term for the conditions. There are also some names for the conditions that have not been searched. Please run the Medline searches again, replacing the Emtree term with the appropriate Medical Subject Heading(s), also adding the missing free text terms.

The Ovid platform was used to perform the searches in all three databases. As suggested, we have re-run the searches with the controlled vocabulary terms, and find the following:

For disease controlled vocabulary terms, searching the Emtree term for MPGN in Medline results in the same number of hits as searching with the MeSH term in Medline, and therefore would not be expected to result in any difference to the articles identified.

Search History (3) View Saved

#	Searches	Results	Runtime	Type	Actions	Annotations
1	glomerulonephritis, Membranoproliferative/	2864	0.03	Advanced	Display Results More	
2	membranoproliferative glomerulonephritis/	2864	0.01	Advanced	Display Results More	
3	1 not 2	0	0.02	Advanced	Save More	

Save Remove Combine with: AND OR

Save All Edit Create RSS Create Auto-Alert View Saved Share Search History

Basic Search Find Citation Search Tools Search Fields **Advanced Search** Multi-Field Search

1 resource selected Hide Change

☒ Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to September 30, 2025

☒ Keyword ☐ Author ☐ Title ☐ Journal

Enter keyword or phrase (* or \$ for truncation)

☒ Map Term to Subject Heading

Limits

Search Term Finder

For treatment controlled vocabulary terms, these only exist as Emtree terms for use in Embase. MeSH terms for the treatments were not identified and therefore would not have contributed to the number of hits.

Search History (2) View Saved

#	Searches	Results	Runtime	Type	Actions	Annotations
1	pegretacepln/	0	0.03	Advanced	Save More	
2	iptacopan/	0	0.00	Advanced	Save More	

Save Remove Combine with: AND OR

Save All Edit Create RSS Create Auto-Alert View Saved Share Search History

Basic Search Find Citation Search Tools Search Fields **Advanced Search** Multi-Field Search

1 resource selected Hide Change

☒ Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to September 30, 2025

☒ Keyword ☐ Author ☐ Title ☐ Journal

Enter keyword or phrase (* or \$ for truncation)

☒ Map Term to Subject Heading

Limits

Search Term Finder

Please see below the searches for Medline using Emtree terms (yellow highlight), as per our original search, compared with the use of MeSH terms where available (blue highlight). The number of hits and the articles are the same (green highlight) as our original search indicating our searches identified all relevant articles.

Searches	Results	Runtime	Type	Actions	Annotations
☐ 1 membranoproliferative glomerulonephritis/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	13952	6.45	Advanced	Display Results More	
☐ 2 pegcetacoplan/ or iptacopan/ or (pegcetacoplan or aspayell or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LN023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart or OMS-906 or OMS906).mp.	331	2.88	Advanced	Display Results More	
☐ 3 1 and 2	21	0.01	Advanced	Display Results More	
☐ 4 Glomerulonephritis, Membranoproliferative/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	13952	4.06	Advanced	Display Results More	
☐ 5 (pegcetacoplan or aspayell or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LN023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart or OMS-906 or OMS906).mp.	331	1.44	Advanced	Display Results More	
☐ 6 4 and 5	21	0.01	Advanced	Display Results More	
☐ 7 3 and 6	0	0.01	Advanced	Save More	

Combine with:

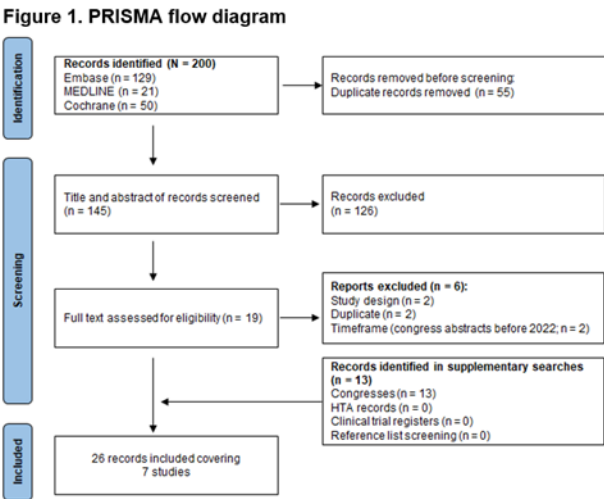
Regarding the inclusion of additional names for the conditions and free-text terms: the search strategy was designed to be comprehensive while maintaining specificity. It includes terminology associated with both C3G and IC-MPGN and the variations in naming conventions for these conditions used across the literature, ensuring coverage of relevant studies. Broad MPGN terms were also used, including unlimited truncation of MPGN which is inclusive of the old classification of the disease. Therefore, we believe our disease search terms have captured all relevant articles for these diseases.

A 3. Please confirm whether the clinical effectiveness searches conducted on MEDLINE (Appendix B; Tables 104 and 107) also included searches of the Epub Ahead of Print, In-Process, In-Data Review & Other Non-indexed Citations, Daily and Versions segments of MEDLINE.

We can confirm that the clinical effectiveness searches conducted in MEDLINE included searches of the Epub Ahead of Print, In-Process, In-Data Review & Other Non-indexed Citations, Daily and Versions segments of MEDLINE

A 4. Appendix E includes details of original searches conducted for the economic searches. While the text states that the original searches were conducted in November 2024, Tables 118-120 provide a search date of 2 September 2024. No information is provided on the update searches conducted in December 2024. Please confirm the dates on which the original searches and the update searches were conducted, provide full strategies for the update searches, and include an updated PRISMA flow diagram to reflect the update searches.

The date of the original search was 2 September 2024 and the date of the updated search was 27 May 2025. The following PRISMA includes both the original and updated searches:



The full search strategies for the original and update search can be found below:

Embase search

Performed 2 September 2024

Details		Search	Embase hits
Disease	1	membranoproliferative glomerulonephritis/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	21 908
Intervention/ comparator	2	pegcetacoplan/ or iptacopan/ or (pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LN023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart or OMS-906 or OMS906).mp.	783
Disease + intervention/ comparators	3	1 and 2	83

Embase <1974 to 2024 August 30>.
ti. searches title, ab. mp., indicates a multi-purpose search including title, abstract, heading word, drug trade name, original title, device or drug manufacturer, device trade name, keyword, floating subject word and candidate term word. '/' indicates a MeSH term.

Performed 27 May 2025

Details		Search	Embase hits
Disease	1	membranoproliferative glomerulonephritis/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated	22 795

		membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	
Intervention/ comparator	2	pegcetacoplan/ or iptacopan/ or (pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LN023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart or OMS-906 or OMS906).mp.	1016
Disease + intervention/ comparators	3	1 and 2	119
Year limit	4	limit 3 to yr="2024 -Current"	46

Embase <1974 to 2025 May 23>.

ti. searches title, ab. mp., indicates a multi-purpose search including title, abstract, heading word, drug trade name, original title, device or drug manufacturer, device trade name, keyword, floating subject word and candidate term word. '/' indicates a MeSH term.

MEDLINE search

Performed 2 September 2024

Details		Search	MEDLINE hits
Disease	1	membranoproliferative glomerulonephritis/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	13 313
Intervention/ comparator	2	pegcetacoplan/ or iptacopan/ or (pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LN023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart or OMS-906 or OMS906).mp.	205
Disease + intervention/ comparators	3	1 and 2	10

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to August 29, 2024>

ti. searches title, ab. mp., indicates a multi-purpose search including title, abstract, heading word, drug trade name, original title, device or drug manufacturer, device trade name, keyword, floating subject word and candidate term word. '/' indicates a MeSH term.

Performed 27 May 2025

Details		Search	MEDLINE hits
Disease	1	membranoproliferative glomerulonephritis/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	13 756
Intervention/ comparator	2	pegcetacoplan/ or iptacopan/ or (pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LN023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart or OMS-906 or OMS906).mp.	293

Disease + intervention/ comparators	3	1 and 2	16
Year limit	4	limit 3 to yr="2024 -Current"	11

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to May 23, 2025>

ti. searches title, ab. mp., indicates a multi-purpose search including title, abstract, heading word, drug trade name, original title, device or drug manufacturer, device trade name, keyword, floating subject word and candidate term word. '/' indicates a MeSH term.

Cochrane search

Performed 2 September 2024

Details		Search	Cochrane hits
Disease	1	membranoproliferative glomerulonephritis/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	965
Intervention/ comparator	2	pegcetacoplan/ or iptacopan/ or (pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LN023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart or OMS-906 or OMS906).mp.	245
Disease + intervention/ comparators	3	1 and 2	36

Databases: EBM R DARE; NHS Economic Evaluation Database; Health Technology Assessment; Cochrane Methodology Register; EBM Reviews - ACP Journal Club <1991 to August 2024>; EBM Reviews - Cochrane Central Register of Controlled Trials <July 2024>; EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 28, 2024>.

Performed 27 May 2025

Details		Search	Cochrane hits
Disease	1	membranoproliferative glomerulonephritis/ or (C3 glomerulopathy or complement 3 glomerulopathy or C3G or dense deposit disease or DDD or C3 glomerulonephritis or C3GN or immune complex membranoproliferative glomerulonephritis or immune complex mediated glomerulonephritis or IC-MPGN or immunoglobulin associated membranoproliferative glomerulonephritis or immunoglobulin-associated MPGN or immunoglobulin mediated membranoproliferative glomerulonephritis or immunoglobulin-mediated MPGN or Ig-MPGN or membranoproliferative glomerulonephritis or MPGN*).mp.	979
Intervention/ comparator	2	pegcetacoplan/ or iptacopan/ or (pegcetacoplan or aspaveli or empaveli or syfovre or APL-2 or iptacopan or fabhalta or LN023 or ARO-C3 or AROC-3 or SAR443809 or BCX10013 or ADX-097 or KP104 or NM8074 or zaltenibart or OMS-906 or OMS906).mp.	279
Disease + intervention/ comparators	3	1 and 2	47
Year limit	4	limit 3 to yr="2024 -Current"	14

Databases: EBM R DARE; NHS Economic Evaluation Database; Health Technology Assessment; Cochrane Methodology Register; EBM Reviews - ACP Journal Club <1991 to April 2025>; EBM Reviews - Cochrane Central Register of Controlled Trials <April 2025>; EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 21, 2025>.

A 5. Please supply the terms used to search for conferences and for HTA reports.

The following terms were searched for in congress abstracts:

- C3 glomerulopathy
- C3G
- C3 glomerulonephritis
- DDD
- dense deposit disease
- IC-MPGN
- immune complex membranoproliferative glomerulonephritis

For identification of HTA reports, the following terms were searched:

- C3 glomerulopathy
- C3G
- C3 glomerulonephritis
- DDD
- dense deposit disease
- IC-MPGN
- immune complex membranoproliferative glomerulonephritis
- membranoproliferative glomerulonephritis
- MPGN

Decision problem

A 6. Priority question. The company stated that: “Overall, the VALIANT and VALE studies were generally representative of a real-world C3G or primary IC-MPGN population with the exception of patients with CKD stages 4 or 5, who were excluded from the study based on their baseline eGFR being <30 ml/min per 1.73 m².” Please clarify if patients with CKD stages 4 or 5 were therefore excluded from the decision problem (DP).

Thank you for this question. Sobi has since done some further clinical interviews to address this and other queries from the EAG. The feedback from UK clinicians was that the patients enrolled in VALIANT broadly reflect the population that clinicians

would consider treating with pegcetacoplan. Due to the VALIANT eligibility criteria, only a small proportion of enrolled patients were in CKD stage 4 (3%), comprising those who had progressed after screening. However, UK clinicians consulted by Sobi indicated they would consider pegcetacoplan in CKD stage 4 patients, particularly where there is evidence of active glomerular disease and no irreversible damage—i.e., where a treatment effect is plausible—or in patients who have demonstrated a response to pegcetacoplan but have slowly progressed from CKD stage 3.

For additional context, outcomes for VALIANT participants who entered the study with CKD stage 4 are summarised in Table 1 below. Subject 42001001 was assigned to the active-treatment arm (pegcetacoplan), whereas the other two subjects received placebo. Although the very small sample size limits inference, the pegcetacoplan-treated subject exhibited more favourable outcomes than the placebo-treated subjects.

Table 1. UPCR outcomes for CKD stage 4 patients in the VALIANT trial

SUBJID	Regimen	UPCR (mg/g; FMV)			
		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%)

Note: The table presents values as observed in the clinical trial. For each scheduled visit, urinary protein measurements were obtained in triplicate, and the results shown represent arithmetic means of those measurements. Estimates for **Week 26** reflect the arithmetic average of data collected during **Weeks 24, 25, and 26**. Results for **one patient (15 years of age)** who prematurely discontinued from the **placebo group** due to an adverse event were excluded from the analysis

Broadly, UK clinicians would not recommend treating CKD stage 5 as the kidneys are likely to be irreversibly damaged, but this would be on a case by case basis as some patients could be on treatment and not on dialysis/transplant. [Personal correspondence, 7 October 2025].

A 7. Priority question. The company stated that: “Eculizumab is not included in the base case analysis due to the limited evidence regarding its widespread use in clinical practise in the UK and lack of robust data confirming its efficacy in stabilising eGFR and reducing uPCR in patients with C3G.” However, no evidence was provided in the CS to validate this statement.

- a) Please provide evidence of the number and percentage of patients currently being treated with eculizumab in England and Wales clinical practice for patients with post-transplant recurrence as specified in the NHS England clinical commissioning policy for eculizumab.**

Whilst eculizumab can be a treatment option for some patients, the use of eculizumab in UK clinical practise is uncommon. The NHS England commissioning policy restricts use to a small subgroup of patients with post-transplant recurrence with a significant decline of transplant function (>20% decline in eGFR within the previous 3 months) (8).

Since the policy was put in place, 7 patients have been treated with eculizumab in the period until March 2023 (9). Meaning, on average, 1 person per year is able to access eculizumab. In contrast, pegcetacoplan can be started as soon as recurrence is diagnosed, in line with the clinical trial evidence and the draft summary of product characteristics (SmPC).

Clinical outcomes data on the above patients receiving eculizumab in UK clinical practise is not available.

- b) Please provide a systematic literature review (SLR) to show the range of evidence available for eculizumab in populations as similar as possible to that specified in the NHS England clinical commissioning policy for eculizumab.**

Due to time constraints and committee agreement during the iptacopan appraisal that eculizumab is not an appropriate comparator, a new SLR for eculizumab was not conducted. However, the original clinical SLR captured 2 studies which specifically explored the use of eculizumab, which were subsequently excluded as eculizumab was not considered a comparator for the majority of the patient

population within the scope of this appraisal. The studies that were identified are listed below, along with an exclusion reason (beyond comparator):

- Patriquin CJ, Kuo KHM. Eculizumab and Beyond: The Past, Present, and Future of Complement Therapeutics. *Transfusion Medicine Reviews* 2019;33(4):256-265. – Would be excluded due to study design and publication type
- Phekoo A, Turk M, Torain J et al. Use of Eculizumab during Pregnancy in a Patient with C3gn. *American Journal of Kidney Diseases* 2024;83(4 Supplement 2):S44. – Would be excluded due to study design (case report)

In addition, a supporting SLR has previously been conducted by the company (and was not provided as part of the original submission) to identify and appraise the available literature relating to current standard of care treatments for C3G and IC-MPGN (10). The SLR was designed to capture all interventions and comparators for C3G and IC-MPGN.

The use of eculizumab was captured in 5 observational studies and an SLR with meta-analysis:

Studies including eculizumab	Disease	Outcome
Borovitz Y, Alfandary H, Dagan A, et al. C3 glomerulopathy in children and adolescents. <i>Journal of the American Society of Nephrology</i> . Conference: Kidney Week 2021;32.	C3G	Of 17 patients treated with SoC (including eculizumab) only 12% achieved complete remission.
Caravaca-Fontan F, De Jorge EG, De Cordoba SR. Therapeutic superiority of mycophenolate mofetil plus steroids in C3 glomerulopathy: A propensity-matched cohort study. <i>Nephrology Dialysis Transplantation</i> . Conference: 56th Annual Congress of the European Renal Association European Dialysis and Transplant Association, ERA EDTA 2019;34.	C3G	49 patients treated with MMF plus steroids were compared with 49 patients treated with cyclophosphamide, rituximab, eculizumab, calcineurin inhibitors or plasmapheresis. Kaplan-Meier analysis showed a significant worse renal survival in patients not treated with MMF.

Caravaca-Fontan F, Diaz-Encarnacion MM, Lucientes L, et al. Mycophenolate mofetil in c3 glomerulopathy and pathogenic drivers of the disease. <i>Clinical Journal of the American Society of Nephrology</i> 2020; 15 :1287-1298.	C3G	Corticosteroids plus MMF was associated with a higher rate of remission and lower probability of kidney failure compared with patients treated with eculizumab
Suarez MLG, Thongprayoon C, Mao MA. Treatment of c3 glomerulopathy in kidney transplant recipients: A meta-analysis. <i>Journal of the American Society of Nephrology</i> . Conference: Kidney Week 2019;30.	C3G	The pooled estimated rates of allograft loss among kidney transplant patients with C3G were 33% after eculizumab, 42% after therapeutic plasma exchange, and 81% after rituximab.
Welte T, Arnold F, Westermann L, Rottmann FA et al. Eculizumab as a treatment for C3 glomerulopathy: a single-center retrospective study. <i>BMC Nephrology</i> 2023; 24 .	C3G	After eculizumab treatment, 5 patients showed a stable outcome, 6 patients showed a negative outcome. Among patients receiving SoC, one patient showed a stable outcome, two patients showed a negative outcome.
Aksoy E, Mirioglu S, Uludag O, et al. Comparison of various features and outcomes in adult patients with immune complex membranoproliferative glomerulonephritis and C3 glomerulopathy. <i>Nephrology Dialysis Transplantation</i> . Conference: 56th Annual Congress of the European Renal Association European Dialysis and Transplant Association, ERA EDTA 2019;34.	C3G + IC-MPGN	Eculizumab was used in 2 patients with C3G.

Overall, the findings show the benefit of eculizumab in chronic progressive C3G and IC-MPGN is limited.

c) If appropriate clinical effectiveness evidence is found, then please conduct a comparison with pegcetacoplan on all available outcomes.

Due to time constraints and committee agreement during the iptacoplan appraisal that eculizumab is not an appropriate comparator, as well as the lack of eculizumab data, a comparison with pegcetacoplan was not deemed feasible.

Clinical effectiveness evidence

A 8. Priority question. Tables are presented in the CS to show the number and percentage of patients who received each type of concomitant therapy in the VALIANT trial.

a) Please provide these data for each of the following key subgroups:

- i. Primary C3G pre-transplant**
- ii. Primary C3G post-transplant**
- iii. Primary IC-MPGN pre-transplant**
- iv. Primary IC-MPGN post-transplant**

b) Please provide similar data for England and Wales clinical practice, and comment on the comparison between these data and those for the VALIANT trial.

Thank you for the request. In response to part A of this question, we have included in our response data on concomitant medication use (as a part of standard of care) in the VALIANT trial for the four requested subgroups, both during the randomised controlled period and open-label period.

i. C3G pre-transplant

Concomitant medications as standard of care during the RCP

	Pegcetacoplan (N = 46) n (%)	Placebo (N = 42) n (%)	Overall (N = 88) n (%)
ACEi/ARB	43 (93.5)	37 (88.1)	80 (90.9)
Immunosuppressants	32 (69.6)	27 (64.3)	59 (67.0)
Corticosteroids for systemic use	17 (37.0)	12 (28.6)	29 (33.0)
SGLT2 inhibitors	7 (15.2)	3 (7.1)	10 (11.4)

Concomitant medications as standard of care during the OLP

	Pegcetacoplan-to-pegcetacoplan (N = 44) n (%)	Placebo-to-pegcetacoplan (N = 38) n (%)	Overall (N=82) n (%)

ACEi/ARB	42 (95.5)	33 (86.8)	75 (91.5)
Immunosuppressants	28 (63.6)	24 (63.2)	52 (63.4)
Corticosteroids for systemic use	14 (31.8)	11 (28.9)	25 (30.5)
SGLT2 inhibitors	5 (11.4)	3 (7.9)	8 (9.8)

ii. C3G post-transplant

Concomitant medications as standard of care during the RCP

	Pegcetacoplan (N = 5) n (%)	Placebo (N = 3) n (%)	Overall (N = 8) n (%)
ACEi/ARB	4 (80.0)	3 (100.0)	7 (87.5)
Immunosuppressants	5 (100.0)	3 (100.0)	8 (100.0)
Corticosteroids for systemic use	5 (100.0)	3 (100.0)	8 (100.0)
SGLT2 inhibitors	1 (20.0)	1 (33.3)	2 (25.0)

Concomitant medications during the OLP

	Pegcetacoplan-to- pegcetacoplan (N = 5) n (%)	Placebo-to- pegcetacoplan (N = 3) n (%)	Overall (N = 8) n (%)
ACEi/ARB	5 (100.0)	3 (100.0)	8 (100.0)
Immunosuppressants	5 (100.0)	3 (100.0)	8 (100.0)
Corticosteroids for systemic use	5 (100.0)	3 (100.0)	8 (100.0)
SGLT2 inhibitors	1 (20.0)	1 (33.3)	2 (25.0)

iii. Primary IC-MPGN pre-transplant

Concomitant medications as standard of care for during the RCP

	Pegcetacoplan (N = 12) n (%)	Placebo (N = 15) n (%)	Overall (N = 27) n (%)
ACEi/ARB	10 (83.3)	15 (100.0)	25 (92.6)
Immunosuppressants	10 (83.3)	11 (73.3)	21 (77.8)
Corticosteroids for systemic use	4 (33.3)	8 (53.3)	12 (44.4)
SGLT2 inhibitors	1 (8.3)	1 (6.7)	2 (7.4)

Concomitant medications for the OLP

	Pegcetacoplan-to- pegcetacoplan (N = 12) n (%)	Placebo-to- pegcetacoplan (N = 15) n (%)	Overall (N = 27) n (%)
ACEi/ARB	10 (83.3)	11 (73.3)	21 (77.8)

Immunosuppressants	7 (58.3)	9 (60.0)	16 (59.3)
Corticosteroids for systemic use	3 (25.0)	7 (46.7)	10 (37.0)
SGLT2 inhibitors	1 (8.3)	1 (6.7)	2 (7.4)

iv. Primary IC-MPGN post-transplant

Concomitant medications as standard of care for during the RCP

	Pegcetacoplan (N = 0) n (%)	Placebo (N = 1) n (%)	Overall (N = 1) n (%)
ACEi/ARB	0 (0.0)	1 (100.0)	1 (100.0)
Immunosuppressants	0 (0.0)	1 (100.0)	1 (100.0)
Corticosteroids for systemic use	0 (0.0)	1 (100.0)	1 (100.0)
SGLT2 inhibitors	0 (0.0)	1 (100.0)	1 (100.0)

Concomitant medications for the OLP

	Pegcetacoplan-to-pegcetacoplan (N = 0) n (%)	Placebo-to-pegcetacoplan (N = 1) n (%)	Overall (N = 1) n (%)
ACEi/ARB	0 (0.0)	1 (100.0)	1 (100.0)
Immunosuppressants	0 (0.0)	1 (100.0)	1 (100.0)
Corticosteroids for systemic use	0 (0.0)	1 (100.0)	1 (100.0)
SGLT2 inhibitors	0 (0.0)	1 (100.0)	1 (100.0)

For part B of this response, medication use for C3G and IC-MPGN in UK clinical practise was extracted from a publication reporting from the RaDaR registry (<https://www.ukkidney.org/rare-renal/aboutdata>). (Masoud et al., Kidney International (2025)108, 455–469; <https://doi.org/10.1016/j.kint.2025.06.003>).

Of the 371 incident patients enrolled in the RaDaR registry, 38% (n=42) with C3GN, 42% (n=22) with dense deposit disease (DDD) and 49% (n=63) of those with IC-MPGN had used immunosuppression within 1-yr of diagnosis. A RAS inhibitor was used by 40% (n=44) with C3GN, 43% (n=23) with DDD and 42% (n=54) with IC-MPGN, within 1-yr of diagnosis. Table 1 from the publication shows that the data was not segregated into medication use pre- or post-transplant.

Table 1 | Baseline demographics and outcomes

	C3G					
	C3GN		DDD		IC-MPGN	
	N = 138	(%)	N = 65	(%)	N = 168	(%)
Age at diagnosis, yr, n	138		65		168	
Median (IQR)	24 (14–46)		14 (10–34)		25 (10–54)	
Pediatric (<18 yr)	50	(36)	41	(63)	73	(43)
Sex, n	138		65		168	
Female	54	(39)	31	(48)	81	(48)
Ethnicity, n	126		58		157	
White	113	(90)	47	(81)	139	(89)
Median follow up duration, n	138		65		168	
Median (IQR), yr	10.6 (9.4–11.2)		10.6 (8.9–18.0)		12.0 (7.5–15.6)	
Serum albumin at diagnosis, n	60		38		92	
Mean (SD), g/l	32 (10)		29 (8)		28 (8)	
Complement C3 levels at diagnosis, n	48		27		45	
Median (IQR), g/l	0.41 (0.20–1.01)		0.36 (0.12–0.73)		0.64 (0.17–0.94)	
Complement C4 levels at diagnosis, n	48		26		44	
Median (IQR), g/l	0.25 (0.16–0.33)		0.22 (0.15–0.31)		0.14 (0.09–0.25)	
Kidney failure event, n	138		65		168	
Yes	57	(41)	29	(45)	62	(37)
Immunosuppression within 1 yr of diagnosis, n	110		53		129	
Yes	42	(38)	22	(42)	63	(49)
RAS inhibitor within 1 yr of diagnosis, n	110		53		129	
Yes	44	(40)	23	(43)	54	(42)

Concomitant medication use in VALIANT was higher overall compared to the RaDaR study. However, the RaDaR study listed medication use within 1 year of diagnosis and not the overall number on standard of care at data collection, making it difficult to compare with the VALIANT trial.

It is notable that whilst immunosuppressant use was high in VALIANT (65% of patients with C3G and 67% with IC-MPGN) a subgroup analysis of patients in VALIANT on concomitant immunosuppressive (IS) therapy, demonstrated favourable efficacy regardless of their IS treatment status. Both groups achieved eGFR stabilization (+6.8 and +5.0 mL/min/1.73 m² vs placebo in IS-treated and non IS-treated patients, respectively and there was a 70.3% and 64.5% clinically meaningful proteinuria reduction vs placebo in IS-treated and non IS-treated patients, respectively).

The number of post-transplant patients from the VALIANT study were small (n=8 for C3G and n=1 for IC-MPGN). All post-transplant patients were on immunosuppressant therapy, but the proportion on a RAS inhibitor was similar to the pre-transplant group. As the RaDaR study did not segregate pre-and post-transplant it is not possible to comment on how these data compare with UK clinical practice.

Indirect treatment comparison (ITC)

A 9. Priority question. NOBLE is a randomised controlled trial (RCT) that compared pegcetacoplan plus standard of care (SoC) with SoC, which is the same comparison as in VALIANT.

a) Please explain why NOBLE was excluded from the ITC.

b) Please conduct a network meta-analysis (NMA), which includes VALIANT, NOBLE and APPEAR-C3G.

Thank you for your question. Although NOBLE was part of the pegcetacoplan clinical trial programme, the study was excluded from the ITC due to several key differences from VALIANT and APPEAR-C3G. The population of NOBLE was restricted to post-transplant patients, whereas APPEAR-C3G included only native disease and VALIANT included both, which meant the populations did not overlap. Given the trial enrolled only 13 patients (10 pegcetacoplan, 3 standard of care), the sample size was considered too small for reliable statistical inference and insufficient to conduct an MMRM analysis, consistent with the statistical method used in both VALIANT and APPEAR C3G. The central limit theorem does not apply making effect estimates unstable and poorly generalisable. Additionally, NOBLE was open-label, lacked blinding and had a different primary endpoint (histology vs proteinuria reduction), with proteinuria only assessed descriptively. Outcome definitions and statistical methods therefore differ substantially from VALIANT and APPEAR-C3G. The follow-up duration of the randomised period was also significantly shorter (12 weeks) compared to VALIANT and APPEAR-C3G (6 months). Taken together, these factors make NOBLE unsuitable for inclusion in the ITC.

Table 2. Comparison of trial characteristics for pegcetacoplan and iptacopan

Feature	VALIANT	APPEAR-C3G	NOBLE	Justification for exclusion of NOBLE
Population	• C3G or IC-MPGN	• C3G • Native only	• C3G • Post-transplant	• Transplant population may have different prognosis,

	Native and post-transplant			treatment response, and disease biology than native disease. No overlapping populations between NOBLE and APPEAR-C3G
Sample size	Large - PEG (n=63) - PLB (n=61)	Moderate - IPTA (n=38) - PLB (n=36)	Small - PEG (n=10) - PLB (n=3)	The NOBLE trial enrolled only 13 patients, an insufficient sample size for reliable statistical inference. With so few patients, the central limit theorem does not apply making treatment effect estimates unstable, uncertain, and poorly generalizable.
Study design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, open-label	Lack of blinding reduces the possibility for a credible comparison.
Primary endpoint	Proteinuria reduction (UPCR) – MMRM analysis	Proteinuria reduction (UPCR) – MMRM analysis	Histology (change in C3c staining) [Proteinuria reduction assessed as a	Outcome definitions are consistent between VALIANT and APPEAR-C3G, but differ substantially from

			secondary outcome - descriptive statistics]	NOBLE in terms of analysis duration and statistical methodology. The small sample size in NOBLE is insufficient for MMRM analysis and does not ensure reliable estimates, as the central limit theorem does not apply.
Follow up for RCT	28 weeks (DB)	6 months (DB)	12 weeks (OL)	

A 10. Priority question. The ITC compares the addition of pegcetacoplan to SoC with the addition of iptacopan to SoC via the common comparator of SoC. However, the nature of SoC in each of the trials varies.

- a) Please provide a comparison of the percentages of patients who received each of the SoC treatments between all of the RCTs i.e. VALIANT, NOBLE and APPEAR-C3G.**
- b) Please comment on the effect on outcomes of any differences between the RCTs.**

As stated in the company submission, there are no currently recommended therapies to treat C3G in UK practice. Management is largely supportive, focusing on blood pressure control (commonly via ACE inhibitors or ARBs), and in selected patients, SGLT-2 inhibitors, corticosteroids or immunosuppressants such as mycophenolic acids. These therapies are used to slow disease progression, but evidence of efficacy is limited as they are unable to address the disease's underlying mechanisms.

Iptacopan is currently undergoing NICE appraisal, with an expected publication date in January 2026. Across pegcetacoplan and iptacopan trials, background standard of care is broadly similar, with both APPEAR-C3G and VALIANT showing predominant

use of RAAS inhibitors and corticosteroids. APPEAR-C3G reports on-study use of mycophenolic acid, whereas VALIANT captures a broader range of immunosuppressants, including agents such as tacrolimus, and also enrolled post-transplant patients. Use of SGLT-2 inhibitors and other antihypertensives was minimal in both trials.

These differences in standard of care, particularly regarding the type and breadth of immunosuppressants used and the inclusion of post-transplant patients in VALIANT, should be considered when interpreting the indirect treatment comparison.

Nevertheless, the broadly similar use of RAAS inhibitors and corticosteroids suggests that these variations are unlikely to materially affect the incremental treatment effects observed. As such, while methodological and population differences should be acknowledged, they are not expected to introduce significant bias into the ITC results.

It should be noted that iptacopan has shown a decreased effect in patients treated with concomitant immunosuppressants (Iptacopan, SmPC

www.ema.europa.eu/en/documents/product-information/fabhalta-epar-product-information_en.pdf) which is not the case for pegcetacoplan, where there is no difference in efficacy in patients with or without immunosuppression. Therefore, the difference in the proportion of patients with immunosuppression is a factor that may overestimate the efficacy of iptacopan relative to pegcetacoplan in a comparison.

Medication Category	VALIANT (%)	APPEAR-C3G (%)	NOBLE (%)	Key Comment
RAS inhibitors	91	97-100	100	High in all trials. Comparable background therapy
Immunosuppressants	69	37 (MPA only allowed)	100	VALIANT & NOBLE includes broader immunosuppressants (tacrolimus, mycophenolate mofetil, ciclosporin). More patients were receiving immunosuppressants.
Corticosteroids for systemic use	32-39	29-36	78	Similar proportions in VALIANT & APPEAR
SGLT2i	9-10	5-6	0	Minimal use; slightly higher in VALIANT

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker, MPA, mycophenolic acid; SGLT2i, sodium glucose cotransporter-2 inhibitor.

Section B: Clarification on cost-effectiveness data

Population

B 1. Priority question. According to the CS “Subgroup analyses in VALIANT showed consistent treatment effects across C3G and IC-MPGN, adults and adolescents, and post- versus non-transplant patients, with no statistically significant differences observed in key proteinuria and eGFR results. Given this consistency, and recognising the rarity of the conditions and limited subgroup sizes, subgroup analyses are not expected to significantly impact the economic analysis either”. The EAG considers the justification provided for not performing subgroup analyses in the economic model insufficient. Even in the absence of differential efficacy, differences in cost-effectiveness may arise from variations in baseline risks, HRQoL, resource use or costs. Therefore, please provide subgroup analyses as specified in the NICE final scope.

Please find the baseline characteristics identified for each of the sub-groups of patients in Table 3 to Table 5. These statistics were used to generate scenario analysis for each of the six identified sub-groups - C3G and IC-MPGN, adults and adolescents, and post- versus non-transplant patients

Table 3: Baseline characteristics for C3G/primary IC-MPGN sub-groups

Characteristic	C3G N = 96 ¹	IC-MPGN N = 28 ¹
Age	26.78	23.18
Baseline Weight (kg)	63.58	61.43
Sex		
F	57.29%	53.57%
M	42.71%	46.43%
CKD stages		
CKD 1	46.88%	42.86%
CKD 2	19.79%	25.00%
CKD 3	29.17%	32.14%
CKD 4	4.17%	0.00%
uPCR_FMV_levels		
<1g/g	11.46%	0.00%

Characteristic	C3G N = 96 ¹	IC-MPGN N = 28 ¹
1-3 g/g	60.42%	53.57%
≥3 g/g	28.13%	46.43%
Pooled Age Group 1		
Adolescent (12 to 17 years)	39.58%	60.71%
Adult (≥ 18 years)	60.42%	39.29%
Stratification Group 1		
non-transplant	91.67%	96.43%
post-transplant recurrence	8.33%	3.57%

¹Mean; %

Table 4: Baseline characteristics for adults/adolescents sub-groups

Characteristic	Adolescent (12 to 17 years) N = 55 ¹	Adult (≥ 18 years) N = 69 ¹
Age	14.69	34.96
Baseline Weight (kg)	56.51	68.34
Sex		
F	58.18%	55.07%
M	41.82%	44.93%
CKD_stages		
CKD 1	60.00%	34.78%
CKD 2	20.00%	21.74%
CKD 3	18.18%	39.13%
CKD 4	1.82%	4.35%
uPCR_FMV_levels		
<1g/g	12.73%	5.80%
1-3 g/g	54.55%	62.32%
≥3 g/g	32.73%	31.88%
Analysis-Disease Type (Screening Biopsy)		
C3G	69.09%	84.06%
IC-MPGN	30.91%	15.94%
Stratification Group 1		
non-transplant	98.18%	88.41%
post-transplant recurrence	1.82%	11.59%

¹Mean; %

Table 5: Baseline characteristics for non-transplant/post-transplant recurrence sub-groups

Characteristic	non-transplant N = 115 ¹	post-transplant recurrence N = 9 ¹
Age	24.63	43.00
Baseline Weight (kg)	62.95	64.94
Sex		
F	59.13%	22.22%
M	40.87%	77.78%
CKD_stages		

Characteristic	non-transplant N = 115 ¹	post-transplant recurrence N = 9 ¹
CKD 1	49.57%	0.00%
CKD 2	20.00%	33.33%
CKD 3	27.83%	55.56%
CKD 4	2.61%	11.11%
uPCR_FMV_levels		
<1g/g	8.70%	11.11%
1-3 g/g	58.26%	66.67%
≥3 g/g	33.04%	22.22%
Analysis-Disease Type (Screening Biopsy)		
C3G	76.52%	88.89%
IC-MPGN	23.48%	11.11%
Pooled Age Group 1		
Adolescent (12 to 17 years)	46.96%	11.11%
Adult (≥ 18 years)	53.04%	88.89%

¹Mean; %

Table 6 to Table 11 provide summaries of the deterministic model results for each of the sub-group population. In each scenario, efficacy with regards to UPCR transitions and estimated eGFR decline were assumed to remain the same as for the full VALIANT population due to similarities in these outcomes highlighted in the CS (Section 2.8).

Table 6 and Table 7 illustrate model outcomes using baseline patient characteristics of the IC-MPGN and C3G patient sub-groups from VALIANT. All other model parameters were assumed to remain constant across the two patient sub-groups.

Table 6: Scenario analysis - IC-MPGN sub-group

	Pegcetacoplan	Standard of care	Iptacopan
Total			
Costs			
QALYs			
Lys	50.348	44.747	47.144
Incremental			
Costs			
QALYs			
Lys		5.602	3.205
Cost-effectiveness			
ICER (£/QALY)		£34,572	Dominant
NHB (at £20,000/QALY)		-5.034	99.203
NHB (at £30,000/QALY)		-1.053	66.986
Fully incremental ICERs			
Versus referent	£34,572	Referent	Dominated
Versus next least costly	£34,572	Referent	Dominated

Table 7: Scenario analysis - C3G sub-group

	Pegcetacoplan	Standard of care	Iptacopan
Total			
Costs			
QALYs			
Lys	47.288	41.521	44.139
Incremental			
Costs			
QALYs			
Lys		5.767	3.148
Cost-effectiveness			
ICER (£/QALY)		£36,303	Dominant
NHB (at £20,000/QALY)		-5.450	97.526
NHB (at £30,000/QALY)		-1.405	65.825
Fully incremental ICERs			
Versus referent	£36,303	Referent	Dominated
Versus next least costly	£36,303	Referent	Dominated

Table 8 and Table 9 present model outcomes based on the baseline characteristics of the non-transplant and post-transplant patient subgroups from VALIANT. Due to time constraints, the post-transplant scenario was developed by adjusting the base-case analysis in two key ways. First, post-transplant-specific patient characteristics from VALIANT were incorporated. Second, costs were modified so that all patients incurred post-transplant costs from the start of the model. This was achieved by embedding these costs directly within the UPCR/CKD health state costs and setting the separate “post-transplant cost” input to zero to avoid double-counting. No expected differences in QOL between the two sub-groups were anticipated following expert clinical feedback.

Table 8: Scenario analysis - nontransplant sub-group

	Pegcetacoplan	Standard of care	Iptacopan
Total			
Costs			
QALYs			
Lys	49.440	43.675	46.204
Incremental			
Costs			
QALYs			
Lys		5.764	3.236
Cost-effectiveness			
ICER (£/QALY)		£35,531	Dominant
NHB (at £20,000/QALY)		-5.306	98.581
NHB (at £30,000/QALY)		-1.260	66.552
Fully incremental ICERs			

Versus referent	£35,531	Referent	Dominated
Versus next least costly	£35,531	Referent	Dominated

Table 9: Scenario analysis - post-transplant sub-group

	Pegcetacoplan	Standard of care	Iptacopan
Total			
Costs			
QALYs			
Lys	30.455	25.788	28.366
Incremental			
Costs			
QALYs			
Lys		4.668	2.089
Cost-effectiveness			
ICER (£/QALY)		£58,199	Dominant
NHB (at £20,000/QALY)		-10.250	84.074
NHB (at £30,000/QALY)		-5.044	56.678
Fully incremental ICERs			
Versus referent	£58,199	Referent	Dominated
Versus next least costly	£58,199	Referent	Dominated

Table 10 and Table 11 present model outcomes based on the baseline characteristics of the adolescent and adult patient subgroups from VALIANT. No additional modifications were made for the adult subgroup. For the adolescent analysis, higher healthcare resource use (HCRU) — specifically nephrologist visits and blood tests — was assumed based on expert feedback from paediatric clinicians treating C3G/IC-MPGN patients. In particular, patients in CKD stages 4–5 with UPCR <1.0 g/g or in stable disease, as well as those in CKD stages 1–3 with UPCR 1.0-3.0 g/g, were assumed to require visits every 8 weeks. Patients in CKD stage 1-3 with UPCR >3.0 g/g were assumed to require visits every 5 weeks. Patients in CKD stage 5 with UPCR >1.0 g/g were assumed to require visits every 2 weeks. In addition, the distribution of dialysis modalities was updated based on paediatric clinical input, with the split between haemodialysis and peritoneal dialysis assumed to be approximately 50/50 in the adolescent population. Due to limited alternative values available from the literature, a conservative assumption of no differences in QOL between the two sub-groups was included. This was considered conservative following expert clinical feedback which suggested there may be a greater QOL impact on adolescents in terms of schooling, psychological belonging, impact of stunted skeletal/neurocognitive development which were not able to be captured due to lack of alternative data in the literature.

Table 10: Scenario analysis - adolescent sub-group

	Pegcetacoplan	Standard of care	Iptacopan
Total			
Costs			
QALYs			
Lys	58.760	54.055	55.880
Incremental			
Costs			
QALYs			
Lys		4.705	2.880
Cost-effectiveness			
ICER (£/QALY)		£26,916	Dominant
NHB (at £20,000/QALY)		-2.519	102.974
NHB (at £30,000/QALY)		0.749	69.548
Fully incremental ICERs			
Versus referent	£26,916	Referent	Dominated
Versus next least costly	£26,916	Referent	Dominated

Table 11: Scenario analysis - adult sub-group

	Pegcetacoplan	Standard of care	Iptacopan
Total			
Costs			
QALYs			
Lys	39.788	34.211	37.023
Incremental			
Costs			
QALYs			
Lys		5.576	2.765
Cost-effectiveness			
ICER (£/QALY)		£40,510	Dominant
NHB (at £20,000/QALY)		-6.387	93.668
NHB (at £30,000/QALY)		-2.182	63.180
Fully incremental ICERs			
Versus referent	£40,510	Referent	Dominated
Versus next least costly	£40,510	Referent	Dominated

B 2. The patient population included in the CS consists of adolescents (aged 12-17 years) weighing at least 42 kg and adult patients with primary C3G or IC-MPGN. CS Table 61 reports the baseline characteristics applied in the economic model, which were sourced from the VALIANT trial.

- a) The modelled patient population in CS section 3.2.1 specifically states that patients should at least weigh 42 kg, whereas CS Table 2 suggests that pegcetacoplan can be administered to patients of at least 35 kg. Please comment on this discrepancy.

- b) The majority of patients in VALIANT are in early CKD stages (i.e., only 3.23% of patients had CKD stage 4 at baseline and no patients had CKD stage 5). Additionally, approximately 77% of patients (96/124) in VALIANT had C3G disease, and 23% of patients IC-MPGN (28/124). Please justify whether the VALIANT patient population is representative of the UK C3G and IC-MPGN patient populations (i.e., in terms of HRQoL, resource use and costs, composition of the SoC basket).
- c) Please elaborate on the generalisability of the baseline characteristics reported in CS Table 61 to UK clinical practice.
- d) Please provide a comparison of baseline characteristics from VALIANT (pegcetacoplan) and APPEAR-C3G (iptacopan) and comment on the (implications of) observed differences.
- e) In CS Table 61 it is stated that weight is used in the economic model to inform SoC basket costs. However, CS Tables 2 and 8 suggest that pegcetacoplan dosing is also weight-dependent. Please justify whether weight from VALIANT was also used to model pegcetacoplan dosing and costs.

a) Thank you for bringing this to our attention. Regarding part A, we can confirm there was an error in Section 3.2.1 of CS. Pegcetacoplan can in fact be administered to patients (adolescents) weighing $\geq 30\text{kg}$ with the recommended dose adjustment laid out in Table 2 of the CS.

b) Following KOL opinion sought in response to clarification questions, it was highlighted that the baseline characteristics from VALIANT are broadly aligned with the expected population who will receive pegcetacoplan in clinical practice for the treatment of C3g/IC-MPGN. However, in real-world practice a slightly higher share of patients is anticipated at CKD stage 4.

With respect to generalisability of HRQOL from VALIANT to the UK C3G/IC-MPGN population, please see response to B20a in which expert clinical opinion was sought on this matter.

Healthcare resource use were not collected in VALIANT, however, given expert clinical feedback indicated baseline characteristics aligned with expected clinical practice, and clinical feedback received prior to submission had a large influence on the HCRU used in the model, it is considered the HCRU used on the model also reflects UK general practice.

Concerning how representative the SOC basket from VALIANT – also used in the model – is to UK clinical practice, please refer to response B6a within which expert clinical feedback was received in relation to this.

c) KOL opinion sought in response to clarification questions, highlighted that the baseline characteristics from VALIANT are aligned with the expected population who will receive pegcetacoplan in clinical practice for the treatment of C3G/IC-MPGN. Further detail to this response can be found in the response to question A6.

d) Table 12 summarises the available baseline characteristics from both the VALIANT and APPEAR-C3G studies. When clinicians reviewed this comparison, they noted that the VALIANT study had a lower mean baseline eGFR, indicating that patients in this cohort had slightly more advanced kidney impairment than those in APPEAR-C3G. Clinicians explained that this difference could reasonably lead to expectations of better outcomes in APPEAR-C3G, as patients with less severe disease are likely to experience slower progression. They further emphasised that initiating effective treatment for C3G/IC-MPGN earlier in the disease course is associated with improved outcomes, as it reduces the risk of irreversible kidney damage

Table 12: Baseline characteristics from VALIANT and APPEAR-C3G

Parameter	VALIANT	APPEAR-C3G	
Baseline age, years	26.0	27.9	
Proportion female	56.5%	36.5%	
Mean eGFR, mL/min/1.73m ²	82.8	92.8	
CKD stage 1	45.97%	58.1%	
CKD stage 2	20.97%	23.0%	
CKD stage 3a	29.84%	6.8%	16.3%
CKD stage 3b		9.5%	
CKD stage 4	3.23%	2.7%	

e) As the modelled cohort began at a starting age of approximately 25 years, dosing was assumed to be consistent across all patients, with adults receiving 1,080 mg of pegcetacoplan twice weekly. Furthermore, baseline characteristics for the adolescent subgroup scenario (see response to B1) indicated an average weight greater than 50 kg; therefore, this cohort was also assumed to receive the same 1,080 mg twice-weekly dose.

Due to time constraints and the volume of clarification requests, it was not feasible to implement the structural model modifications required to adjust dosing based on patient weight. However, as data from the VALIANT study showed no significant differences in outcomes between adult and adolescent populations, any potential dose reduction for patients weighing less than 50 kg would primarily affect treatment costs. In clinical practice, it is expected that adolescents requiring lower doses would still require a whole vial (including 100% wastage), therefore there is not anticipated to be any impact on the economic analysis when accounting for lower doses for adolescents weighing <50kg.

B 3. The economic model assumes that patients return to the baseline distribution of uPCR levels from VALIANT following a transplant (CS Table 61).

a) Please justify this assumption and provide supporting evidence.

b) Please reconcile the differences between CS Table 61 (baseline distribution) and CS Table 75 (post-transplant distribution, e.g. showing fewer patients in CKD 1). Please clarify which distribution is applied in the base-case, and why.

a) Thank you for your question. Due to the lack of identified literature assessing patient UPCR outcomes post-transplant expert clinical feedback was sought to respond to this question. From these discussions it was established that the original assumption of returning to baseline distributions from VALIANT lacked clinical plausibility as patients are expected to have minimal proteinuria immediately following a transplant beyond low-level leakage from residual native kidneys. In response to this feedback, the Company would like to amend their base case assumptions accordingly.

The new Company base case assumes that at the time of the transplant, all patients have a UPCR <1.0 g/g. In the subsequent cycle, 62.46% of patients are assumed to be in the UPCR <1.0 g/g sub-group, and 37.54% in the UPCR 1.0-3.0 g/g health state. This assumption is based on the expected rate of increase in proteinuria seen in the placebo arm of the VALIANT trial, and subsequently used to inform the SOC UPCR transition probabilities.

Using this updated assumption, after 1-year 34.20% of SOC patients will be in the UPCR <1.0 g/g sub-group, 55.82% in the 1.0-3.0 g/g sub-group, and 9.98% in the >3.0 g/g sub-group. Due to high levels of recurrence following transplants seen in the literature these estimates are considered more plausible than the Company's original base case.

A summary of the impact on the model results vs the original submitted base case (see CS) is outlined in Table 13.

Table 13: Summary of change to original model base case (from CS) following updated UPCR distribution following transplant assumptions

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Original CS - Base case					£28,714	Dominant
Updated UPCR post-transplant assumptions					£37,145	Dominant

- b) As described in Section 3.3.2 of the CS, the values presented in Table 75 were derived from post-transplant-specific literature and applied in the model to redistribute patients across CKD health states following transplantation. Clinical feedback indicated that post-transplant CKD stage can vary considerably, largely depending on the condition of the donor organ. Consequently, the analysis by Pruett et al. (2021), which examined data from 4,545 deceased donor kidney transplants, was considered more robust and reliable than the limited transplant data available from the VALIANT study.

The differences in distributions could be hypothesised as being a result of age of patients (VALIANT) and donor kidneys (Pruett et al. 2021) as demonstrated by Pruett et al. 2021 where deceased kidney recipients demonstrated the expected decline in eGFR-1, as donor age increased.

Model structure

B 4. Priority question. The CS includes a cohort-level Markov model with health states defined by eGFR and uPCR levels. CS Figure 19 provides a schematic overview of the model structure.

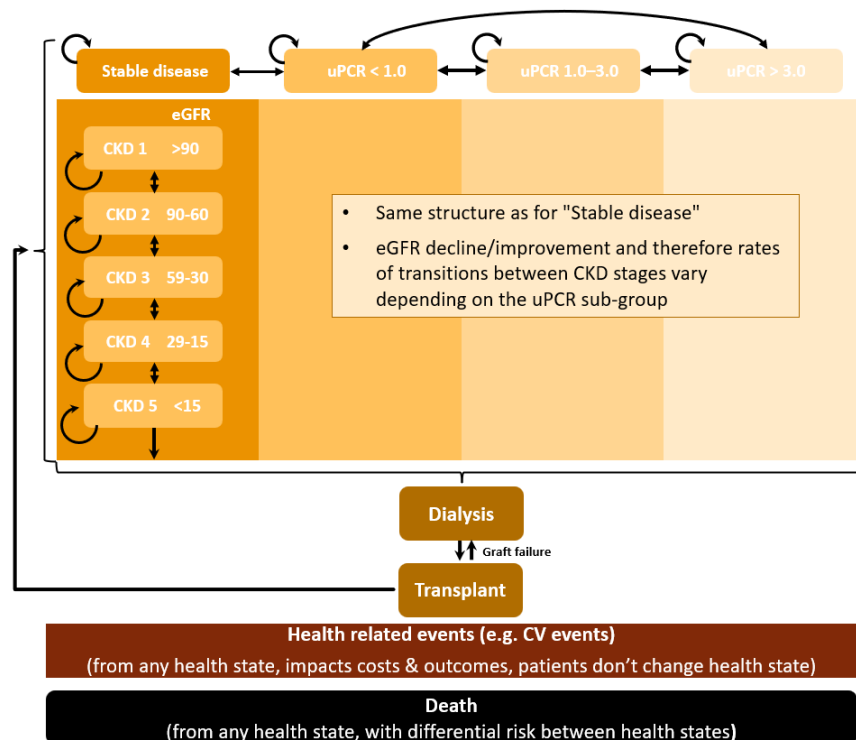
- a) In CS Figure 19, only most frequent transitions are indicated with arrows, despite the statement that “*Technically, transitions between any combination of CKD and uPCR health states are allowed*”. Please provide an updated figure including arrows of all modelled health state transitions.**
- b) Please provide more details on the statement that “*Technically, transitions between any combination of CKD and uPCR health states are allowed*”, e.g. does the model structure allow backward transitions between CKD and/or uPCR states?**
- c) Please elaborate on the plausibility of the statement in b) and whether it is reflective of UK clinical practice.**
- d) In the CS it is stated that a 3-month cycle length is appropriate to capture CKD transitions while minimising variability from short-term eGFR fluctuations. Please provide additional justification why a 3-month cycle length is considered sufficiently short to capture the impact on costs and QALYs as patients progress through the model.**
- e) Please provide a comparison of the current model structure with the model structure of GID-TA11331 (iptacopan for C3G). More specifically, please provide justification and clinical expert opinion for observed differences in terms of the number and types of health states and how**

events such as dialysis, transplantation and cardiovascular events were incorporated.

f) Please provide a comparison of the current model structure with model structures of TAs in the field of CKD, at least including TA942 TA937, TA890, TA882, TA877, TA825, TA809, TA807, TA775, TA623, TA599, TA481, TA358. More specifically, please provide justification for observed differences in terms of cohort versus individual patient modelling, the number and types of health states, the model cycle length, and incorporating events such as dialysis, transplantation and cardiovascular events.

a) Thank you for identifying this discrepancy. Figure 1 illustrates an updated representation of the model structure.

Figure 1: Updated model schematic



b) The model structure allows patients in one UPCR sub-group (UPCR < 1g/g, UPCR 1-3g/g, or UPCR > 3g/g) to transition to any of the other UPCR sub-groups (or remain in the same sub-group) between model cycles. Only patients with UPCR < 1g/g are able to transition to Stable disease.

Within each UPCR sub-group patients can move to an adjacent CKD health state. However, patients can only transition in one direction of CKD progression or improvement, per UPCR sub-group. This is based on anticipated eGFR decline/improvement over time, i.e. if the model assumes patients in a particular UPCR sub-group experience eGFR declines over time, then the cohort can only transition to later CKD health states e.g. CKD 1 to CKD 2 or CKD 2 to CKD 3 etc. for this UPCR sub-group. If the model were to assume an increase in eGFR over time for patients in a specific UPCR sub-group, then patients would only be able to transition to an earlier CKD health state, e.g. CKD 3 to CKD 2 or CKD 2 to CKD 1.

In light of feedback received during the Clarification TC, the number of health states used in the model engines have been streamlined to remove tunnel health states that did not materially impact model outcomes i.e. patients entered a stable disease tunnel state but were immediately treated as being in stable disease, with similar costs and QoL outcomes as someone confirmed to be in stable disease. Therefore, to simplify the number of health states present in the model these tunnel states were removed, with no impact to model outcomes as a result of their removal.

In total, and to provide clarification that was missing from the original CS, there are now 49 health states in the model:

Pre-transplant (25 health states): 4x UPCR sub-group each with 5x CKD health states in each, 4x dialysis [PD, HD, PD unsuitable for transplant, HD unsuitable for transplant], and 1x transplant

Post-transplant (23): 4x UPCR sub-group each with 5x CKD health states in each, 2x dialysis [PD & HD], and 1x transplant

Death (1)

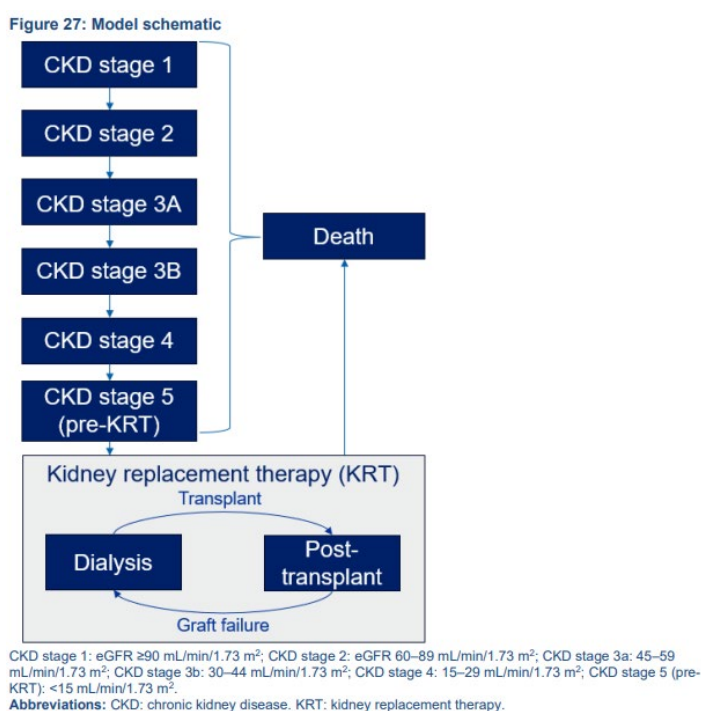
- c) Clinical feedback received prior to submission (CS Appendix L) indicated that long-term improvements in eGFR for this population were unlikely, and therefore do not form the model base case. Due to this, these transitions were

omitted from the original model schematic, despite being considered “technically” possible with the given model structure. Additionally, the linearity of the decline in eGFR employed in the model – dependent on UPCR sub-group – was also supported by UK clinical feedback (CS Appendix L)

Furthermore, clinical data indicates that change in UPCR is bi-directional, with patients seeing increases in UPCR with disease progression, and UPCR decreases with successful treatment. Due to this, the model ensures that patients may transition between any of the UPCR sub-groups, with the exception of stable disease whereby a patient must come from the UPCR <1 sub-group before they can be confirmed as having stable disease.

- d) A 3-month cycle length is consistent with international clinical guidelines (KDIGO 2024), which highlight the extent of short-term variability in eGFR that can confound interpretation over shorter intervals. Specifically, KDIGO 2024 notes that short-term variability in eGFR may arise from a recent acute kidney injury (AKI), and also from transient haemodynamic reductions of 10–20% that are typically observed the first three months of treatment. In people with CKD, changes in eGFR of $\leq 20\%$ over days to weeks are often transient or haemodynamic rather than indicative of structural CKD progression. The guideline further reports that intra-individual biological variation in eGFR is approximately 5%, with a reference-change value of about 14–20% in either direction, and that a ≥ 3 -month persistence threshold is required to confirm a chronic change. The guideline further reports that intra-individual biological variation in eGFR is approximately 5%, with a reference-change value of about 14–20% in either direction, and that a ≥ 3 -month persistence threshold is required to confirm a chronic change.
- e) A breakdown of the key aspects of the model structure and how they compare to the iptacopan appraisal (GID-TA11331) are outlined below. Figure 2 illustrates the model structure used for the iptacopan submission.

Figure 2: Model schematic from GID-TA11331



UPCR

Exclusion of uPCR health states was not fully substantiated in the iptacopan submission, relying only on data on file from model validation exercises. From GID-TA11331: *“While the primary endpoint of APPEAR-C3G was reduction in proteinuria (UPCR), use of this endpoint for economic modelling would have required relying on a surrogacy relationship with clinical outcomes, which is not yet robustly established in quantitative terms for complement inhibitors as a new, disease-modifying class of treatments for C3G.”*

As outlined in CS Section 3.3.1, it is believed and supported by expert UK clinical feedback (CS Appendix L), that there is a large and robust body of evidence to support the relationship between eGFR and UPCR, with changes in UPCR being prognostic of a reduced risk of kidney failure. Due to this, the Company deemed it reasonable to include changes in UPCR within the economic model structure to ensure the primary outcome from VALIANT was captured in the economic analysis.

eGFR

The key difference in use of CKD stages between the two submissions appears to be the split of CKD 3a and CKD 3b in the iptacopan submission.

However, this segmentation appears to only lead to a differentiated number of monitoring visits per year (3 [CKD 3a] vs 4 [CKD 3b]). All other model inputs (costs, QoL, transitions) appear to be equivalent between these two health states.

As NICE CKD guidelines do not differentiate the need for monitoring visits between these health states, and to avoid the added modelling complexity for minimal incremental differences, it was deemed justifiable to combine these two CKD health states within the submission for pegcetacoplan.

Dialysis/transplant

Both submissions – Patients on dialysis have a constant probability of undergoing a transplant.

Iptacopan – Patients initiate dialysis or pre-emptive transplant when eGFR ≤ 7.6 .

Pegcetacoplan – 13.45% undergo pre-emptive transplant 3-months (1-cycle) after reaching CKD 5 (eGFR ≤ 15), remainder assumed to initiate dialysis. This assumption was discussed during UK clinical expert elicitation undertaken following receipt of clarification questions. These clinical expert responses are explored in more detail in response to question B5.

Post-transplant

Both submissions - Patients have a per cycle probability of graft loss.

Iptacopan - Patients enter a single "post-transplant" health state with average costs and QoL assigned to these patients.

Pegcetacoplan – The economic model estimates more granular future costs and QALYs associated with the deterioration of a transplanted kidney. By modelling the deterioration of a transplanted kidney in the same way a native kidney deteriorates the model outcomes are anticipated to more accurately capture the heterogeneity of patients of these rare diseases, in particular

within the PSA outcomes, compared to assigning a singular average cost or QALY for these patients.

CV-events

Iptacopan - CV events were included in a scenario analysis only due to a lack of data identified on the risk of CV events in patients with C3G and clinicians considered that literature from CKD more broadly may overestimate the incidence of CV events.

Pegcetacoplan – CV events are captured as events that incur one-off additional costs and disutility when they occur. Rates of CV-events were identified from literature that observed 637,315 individuals without a history of cardiovascular disease from 24 cohorts (median follow-up 4·2-19·0 years) included in the Chronic Kidney Disease Prognosis Consortium which identified that the addition of eGFR and albumin-to-creatinine ratio significantly improved the discrimination of cardiovascular outcomes beyond traditional risk factors in general populations (Matsushita et al. 2015).

A scenario outlining the impact of removing CV-events has been added to the model. Due to the estimated improvement in LYs for patients on pegcetacoplan, removing CV-event disutilities and costs from the model improves the incremental model outcomes for patients on pegcetacoplan as these (Table 14).

Table 14: Summary of scenario excluding CV-events

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
'New' base case	██████	██████ [↑]	██████	██████	£35,798	Dominant
Removal of CV events	██████	██████ [↑]	██████	██████	£34,980	Dominant

- f) Following expert clinical feedback, it was considered important to focus on prior TAs that had a focus on diseases that had a nephrotic component as it

was highlighted that C3G and IC-MPGN are very distinct in their disease journey as not only do they have a CKD aspect focussing on kidney scarring and loss of function, but also a nephrotic aspect whereby nephrotic syndrome can occur early, fluctuate, and be driven by complement dysregulation. Additionally, the likelihood of recurrence following a transplant is substantially higher in patients with C3G/IC-MPGN due to the underlying, ongoing complement system activity that drives C3G still being present even after a transplant. Therefore, these are important aspects that should be considered in the economic modelling of C3G/IC-MPGN that may not be captured in CKD specific TAs. For these reasons, feedback from clinical expert opinion (11) and the limited timelines for response to clarification questions, only previous TAs in IgAN (TA937 and TA1074) were considered critical sources for comparing model structures in detail.

TA937-Targeted-release budesonide for treating primary IgA nephropathy

The model structure in this appraisal is similar to that employed in the iptacopan appraisal, based on progression through CKD health states before patients initiate dialysis and/or undergo a transplant. Following transplantation patients are assumed to reside in a “post-transplant” health state with average costs and QALYs – similar to GID-TA11331. Due to the similarity in model structures, the rationale for differences in the pegcetacoplan appraisal outlined in response to question B4e also considered to apply to a comparison to TA937.

TA1074 - Sparsentan for treating primary IgA nephropathy

Similar to the model structure submitted as part of the pegcetacoplan appraisal, the model used in TA1074 differentiates patients by both UPCR sub-groups, albeit with differing cut-off thresholds (<0.44g/g, 0.44-0.88g/g, 0.88-1.76g/g, >1.76g/g).

A key difference is the ability for patients to transition from any earlier health state to end-stage renal disease. The rapid and sustained reduction in eGFR required for a patient to go from an early health state (e.g. CKD 1) to ESRD within 3-months was not considered clinically plausible in this or previous

appraisals (TA937). As such, only transitions to neighbouring CKD stages were considered in the appraisal for pegcetacoplan.

Table outlines the differences in key model features across the two prior IgAN appraisals and the current C3G/IC-MPGN appraisal for pegcetacoplan

Table 15: Summary of key model features in current appraisal and previous appraisals in IgAN

Previous evaluations			Current evaluation	
Factor	TA937	TA1074	Chosen value	Justification
Time horizon	Lifetime horizon (56 years, maximum 70 years)	Lifetime horizon (55 years, maximum 71 years)	Lifetime horizon (74 years, maximum 100 years)	As C3G and IC-MPGN are life-long diseases, a lifetime horizon is appropriate to capture all the costs and benefits.
Cycle length	Monthly	12-weekly	3-monthly	VALIANT 24-hour urine collection intervals were undertaken 3-monthly. KDIGO guidelines indicate a ≥ 3 -month persistence threshold is required to confirm a chronic change in eGFR
Model structure	Cohort state-transition model (CKD stage 1-5, dialysis, transplant)	Cohort state-transition model (CKD [stage 1-5], UPCR [4x sub-groups], dialysis, transplant)	Cohort state-transition model (CKD [stage 1-5], UPCR [3x sub-groups], stable disease, dialysis, transplant)	Well defined health states for CKD support this approach. In addition, this structure matches the previous submission for sparsentan.
Treatment waning effect	No waning effect	No waning effect	No waning effect	No evidence to suggest that the efficacy of pegcetacoplan would wane over time.
Source of utilities	Cooper et al. 2020	Cooper et al. 2020	VALIANT and Sidhu et al. 2024	Use of trial data aligns more with NICE reference case. Sidhu et al. selected to prioritise indication specific QoL

				outcomes although Cooper et al. provided as a scenario.
Source of costs	NHS schedule of Reference Costs 2021-2022, eMIT, BNF, Kent et al. 2015	NHS schedule of Reference Costs 2021-2022, eMIT, BNF, Kent et al. 2015	NHS schedule of Reference Costs 2023-2024, eMIT, BNF, Micro-costing approach	Costs from NHS schedule of reference costs, eMIT, and BNF databases chosen in accordance with NICE guidance. Micro-costing approach aligns with NICE preferred methods used in previous IgAN appraisals

B 5. In the economic model it is assumed that 100% of patients transition to dialysis after remaining in CKD stage 5 for one cycle, regardless of treatment received.

- a) Please confirm that this implies that patients are assumed to start dialysis if $\text{eGFR} < 15 \text{ mL/min/1.73m}^2$ (eGFR corresponding to CKD 5).
- b) What is the clinical rationale for this specific threshold for dialysis initiation (of $< 15 \text{ mL/min/1.73 m}^2$)?
- c) Please justify why a different threshold was used compared with other NICE TAs, for instance in GID-TA11331 (considering iptacopan) where patients start kidney replacement therapy (i.e., dialysis and transplant) at $\text{eGFR} < 7.6 \text{ mL/min/1.73 m}^2$.
- d) Please provide an updated economic model and scenario analyses assuming eGFR values of $5 \text{ mL/min/1.73 m}^2$ and $7 \text{ mL/min/1.73 m}^2$ (or the midpoint of $6 \text{ mL/min/1.73 m}^2$) as the threshold for dialysis initiation, in line with NICE guideline NG107 which recommends starting replacement therapy “around $5 \text{ to } 7 \text{ mL/min/1.73 m}^2$ ”.

- e) In clinical practice, some patients may start dialysis at different eGFR values due to complications or comorbidities. Please explain whether and how this was implemented/considered in the economic model.
- f) Please justify the assumption of repeated transplant, and whether this is consistent with clinical practice. Please also elaborate whether it would be more appropriate to cap the maximum number of graft failures and transplants?
- g) Please provide the average modelled number of transplants for pegcetacoplan, SoC and iptacopan, and elaborate on the plausibility of these estimates by providing supporting evidence.
- h) How is the probability of repeated transplant estimated?
- i) Please explain whether a maximum age for a recipient of a transplant was implemented/considered in the economic model, and whether this is clinically plausible.
- j) Is there a distinction between early versus late graft failure in terms of transition probabilities? Please justify why (not)?
- k) Please justify for the following input parameters, whether these are clinically plausible by providing supporting evidence and/or expert opinion:
 - i. Assumption that 100% of patients transition to dialysis after remaining in CKD stage 5 for one cycle, i.e., assuming no pre-emptive transplants.
 - ii. Assumption that median time from starting dialysis to receiving a transplant is 14.4 months.
 - iii. Assumption that 16.8% of patients are unsuitable for transplantation, regardless of the number of prior transplantations.
 - iv. Assumption that 88% of patients undergo haemodialysis and 12% undergo peritoneal dialysis.

- v. Assumption of a 95.32% probability of graft survival.
 - vi. Assumption that patients return to their baseline uPCR levels sourced from VALIANT after a transplant.
- a) Thank you for your question. The model does not use an explicit eGFR threshold at which patients start dialysis. Instead, the model assumes that all patients will either initiate dialysis or undergo a transplant 3-months after entering the CKD 5 health state (i.e. patients only remain in the CKD 5 health state for 1 model cycle. Specifically, the model assumes 13.45% of patients who enter CKD 5 will have a transplant in the next model cycle, with the remaining 86.55% starting dialysis in the next model cycle. Please note that the default model values for proportion of patients moving from CKD 5 to dialysis have been updated from 100% to 86.55% to provide clarification of this split. As the model already assumed those not receiving a transplant would move to dialysis this change in default values had no impact on the model results.
- b) There is no specific eGFR threshold used in the model at which a patient is assumed to start dialysis (see response to B5a). The use of a time-dependant assumption in the model was validated by clinical experts in interviews conducted during the clarification process as being clinically plausible, especially with regards to C3G/IC-MPGN patients, as eGFR is one of many factors considered when identifying patients for kidney replacement therapy (KRT) – as also outlined in the NICE guidelines for. Clinicians highlighted for patients with glomerular disease such as C3G/IC-MPGN, when such patients reach kidney failure, they would often consider kidney replacement therapy at an earlier eGFR threshold than they might for other CKD patients, as the disease may be more progressive and symptoms more severe. Kidney replacement therapy may be commenced when eGFR is approximately 10-15 mL/min/1.73m².
- c) As the model does not utilise an explicit eGFR threshold for initiating dialysis it is not possible to address this question within the given timelines for response due to the extensive nature of changes required to the model structure to account for an eGFR specific threshold.

d) Due to the explicit link between time to dialysis and the model's cycle length, the ability to make modelling updates to reflect alternative scenarios in which eGFR thresholds are varied was not possible in the timeline for responses. However, the model does allow the user to reduce the % of patients entering the dialysis health state from CKD 5. As such, by lowering this value the model is able to keep some patients in CKD 5 for longer than 1 model cycle – as would be the case if an explicit eGFR was used and its threshold was lowered.

A range of alternative % of patients entering dialysis from CKD 5 were explored (50%, 60%, 70%, 80%) to assess the significance of this input on the model results.

Table 16: Summary of scenarios adjusting proportion of patients transitioning from CKD 5 to dialysis

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
'New' base case					£35,798	Dominant
80% of CKD 5 patients initiate dialysis					£35,802	Dominant
70% of CKD 5 patients initiate dialysis					£35,811	Dominant
60% of CKD 5 patients initiate dialysis					£35,823	Dominant
50% of CKD 5 patients initiate dialysis					£35,840	Dominant

- e) Due to the model using time from entering CKD 5 as the key determinant of when a patient starts dialysis it is believed it attempts to more accurately capture the heterogeneity of patients, and when they may initiate dialysis. By using time from entering CKD 5 the model avoids relying on a single threshold eGFR value, which as outlined in the identified NICE guideline NG107 explicitly refers to other reasons why patients may start dialysis before reaching eGFR 5 to 7 ml/min/1.73 m², including:
- i. symptoms of uraemia on daily living, or
 - ii. biochemical measures, or
 - iii. uncontrollable fluid overload
- f) As part of the work to address clarification questions concerning number of transplants in the model the Company undertook additional clinical expert interviews. The interviews identified that repeat transplants over a patient's lifetime are possible, especially when considering the young age at which C3G/IC-MPGN patients are diagnosed. In particular, the experts indicated that the 3.84 estimated in the original model (subsequently updated to 3.66 in the 'new' base case) was deemed plausible when taken in the context of the rapid disease progression seen in C3G/IC-MPNG, younger age at diagnosis, and higher recurrence rate after transplant for these patients.

The decision to cap the number of transplants a patient could receive in the model was considered inappropriate by all four clinicians consulted, as clinical experts noted anecdotally that many patients have three, occasionally some have four, and on rare occasions patients have undergone five transplants or more over their lifetime.

- g) The number of transplants estimated by the model are reported on the "Base case summary" worksheet ('Base case summary'!D104:F104) which are also summarised in Table 17.

Table 17: Number of transplants estimated by the economic analysis, by treatment

	Pegcetacoplan	Standard of care	Iptacopan
Number of kidney transplants in original base case	1.19	3.84	2.11

Number of kidney transplants in 'new' base case	1.17	3.66	2.07

- h) Post-transplant patients are assumed to have specific eGFR and uPCR levels based on the applied post-transplant distributions. The uPCR levels in these patients evolve according to transition matrices that are dependent on the post-transplant treatment received. eGFR progression is then modelled in the same way as at initial model entry, based on the prevailing uPCR level.

Once a patient reaches CKD stage 5 or initiates dialysis, the probability of receiving a transplant is applied. This probability does not differ based on prior transplant history and was reported in CS in the Table 74.

To provide more context, firstly only patients in CKD 5 or on dialysis are eligible to undergo a transplant.

In each health state (CKD 5 or dialysis), patients are assumed to have the same 3-month probability of undergoing a transplant (13.45%), as estimated from median time to transplant of 1.2 years identified from RaDaR data.

This probability is only applied to those on dialysis who are considered eligible and willing to undergo a transplant (84.20%). This assumes 16.80% of dialysis patients are inadequate for kidney transplant, as previously identified for the iptacopan appraisal.

Following a transplant, patients have a constant per-cycle probability of graft survival (95.32%), based on figures from Pruett et al. 2021. Those patients who continue to maintain their graft progress through UPCR and CKD health states as per the native kidney cohort. However, those with graft loss are assumed to return to dialysis.

On returning to CKD 5 or dialysis, the probability of undergoing a transplant is assumed to be the same for all subsequent transplants.

- i) No maximum age for transplant eligibility was implemented or considered in the economic model. While it is true that patients become less likely to be

suitable candidates for kidney transplantation as they age, explicitly modelling older patients with additional stratification based on transplant eligibility and effectiveness would introduce further complexity into an already detailed model.

It is important to note, however, that due to the relatively young starting age of the cohort in the model, introducing a maximum transplant age (e.g., 60 years) would only begin to affect model outcomes after 34 years. Given patient mortality over time and the effects of discounting on costs and outcomes, the impact of such a limitation is expected to be minimal.

- j) Yes, a distinction between early and late graft failure is incorporated in the model. Specifically, early graft failure is informed by Pruett 2021, which reported a 95.32% probability of graft survival. This probability was applied in the first cycle following kidney transplantation to reflect early graft loss.

Beyond the first cycle, graft failure is modelled as a consequence of gradual deterioration of the transplanted kidney, based on post-transplant uPCR and eGFR levels. These levels evolve according to transition probabilities that are dependent on the post-transplant treatment received.

The approach to modelling CKD progression and the transition probabilities used are the same for both pre- and post-transplant patients. What differs are the initial uPCR and eGFR distributions, which are specifically defined for post-transplant patients in the model.

There were no data available to support distinct transition probabilities for pre- versus post-transplant patients. Additionally, results from the VALIANT trial suggested no meaningful differences between these groups, although the sample size of post-transplant patients in the trial was limited.

- k) Expert clinical feedback was obtained following receipt of clarification questions. A summary of the key findings from the discussions is outlined below:

- i. Clinical feedback suggested that the assumption that 100% of patients would initiate dialysis or undergo transplantation within three months of reaching CKD stage 5 was unrealistic for the general CKD population but more plausible for patients with C3G/IC-MPGN, given the rapid decline in kidney function typically observed in these conditions. However, there remains substantial uncertainty regarding the actual proportion of patients who begin dialysis or receive a transplant within this timeframe. Therefore, scenario analyses were conducted in response to B5d to assess the impact of this parameter on the model's outcomes.
- ii. The figure of 14.4 month appeared reasonable to all four clinicians approached for comment.
- iii. The figure of 16.8% of dialysis patients being unsuitable for transplant was considered plausible for the adult population, with no indication other sources might exist. However, this value in paediatrics was considered too high and a value closer to 5% was considered more realistic in practice. Due to this, a value of 5% was used when analysing the adolescents sub-group scenario (see response to B1).
- iv. Without knowledge of alternative values, these figures for the split of HD/PD in the adult population were considered appropriate. However, these figures in the adolescent population were expected to be closer to 50%/50%. As such, this feedback was included in the adolescent scenario analysis conducted in response to B1
- v. The value of 95.32% for graft survival was considered plausible by all clinicians.
- vi. Please see response to B3 for detailed response to KOL feedback on UPCR distributions following a transplant.

Intervention and comparators

B 6. Based on Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines, SoC in the CS includes ACEi/ARB (■■■■%), immunosuppressants (■■■■%), systemic corticosteroids (■■■■%), and SGLT2i (■■■■%). The exact treatment regimens are modelled as components of the SoC basket, along with the proportion of patients receiving each component.

- a) Please justify whether the KDIGO clinical guidelines are in accordance with UK clinical practice.
 - b) Please clarify and justify whether the proportions of patients receiving each SoC component are fixed over time, or whether they can change over time (e.g., are patients allowed to switch between SoC treatments during disease progression)? How does this compare to UK clinical practice?
 - c) Please clarify and justify whether patients can receive multiple SoC treatments simultaneously, or whether monotherapy is assumed? For example, can a patient be on both an ACEi and an ARB? Please compare this to treatment patterns in UK clinical practice.
 - d) If patients can receive multiple SoC treatments simultaneously, please clarify and justify how the combined treatment effect is accounted for in the economic model?
 - e) Please clarify and justify how the effectiveness of each SoC treatment is estimated. In case patients can receive multiple SoC treatments simultaneously, are treatment effects considered additive or how is the combined treatment effect (of multiple SoC components) estimated in the economic model?
 - f) Please elaborate on the implications of the responses to the preceding sub-questions.
- a) Following expert clinical feedback, it was highlighted that the KDIGO guidelines are in the process of being updated. Nevertheless, with regards to

the treatments used in the modelled SOC basket, and the proportion with which they are used, the expert clinical feedback agreed that these are generalisable to UK practice. This feedback was that with the exception of the use of SGLT2i's, which is assumed will be used in more patients in the future, especially in adolescents if the label were to be expanded. The increased uptake of SGLT2i is anticipated to have minimal impact on the model results due to the SOC basket being present in all treatment arms of the model.

- b) It is confirmed that the mix of SOC use over time is fixed across the model time horizon. Since the relative use of each treatment in the SOC basket is inherently linked to the efficacy source (VALIANT), it was considered inappropriate to alter the relative use of each treatment in the basket without also adjusting for the relative efficacy of each treatment. As reported in response to B6a, the relative use of each treatment in the SOC basket was considered generalisable to UK clinical practice by clinical experts interviewed as part of the clarification process.
- c) Following input from clinicians, it was clarified that patients are not expected to receive an ACEi and an ARB simultaneously, which aligns with data from VALIANT in which less than 100% of patients were on ACEi/ARBs. However, clinicians confirmed that patients can receive a combination of ACEi/ARBs and/or immunosuppressants and/or systemic corticosteroids and/or SGLT2i. The relative usage of concomitant medications in VALIANT were considered generalisable to the UK (see response to B6a)
- d) As outlined in previous B6 responses, the distribution of treatments included in the economic analysis were taken directly from concomitant medications used in the economic analysis, and confirmed to be generalisable to the UK. As such, the outcomes from VALIANT implicitly capture the combined treatment effect, at least in the proportions of relative usage seen in VALIANT and applied in the economic model. Therefore, no further adjustment was considered necessary for the placebo arm of the VALIANT trial to ensure it represented outcomes that would be considered generalisable to the UK.

- e) As the treatments included in the SOC basket reflect the concomitant treatments used in VALIANT and the UK C3G/IC-MPGN population, data from the placebo arm of VALIANT were directly used to estimate clinical outcomes for patients in the SOC arm of the economic analysis
- f) Based on responses to the preceding questions, the concomitant treatment data from the placebo arm of VALIANT were considered generalisable to UK clinical practice. Therefore, no adjustments were deemed necessary to account for potential differences in treatment patterns between VALIANT and UK clinical practice that could affect efficacy.

B 7. Please include, consistent with the final scope, eculizumab as a comparator in the economic model for people who have previously had a kidney transplant and who have highly aggressive recurrent disease as specified in the NHS England clinical commissioning policy for eculizumab.

Thank you for your query. As mentioned previously in response to question A7, due to time constraints and committee agreement during the iptacopan appraisal that eculizumab is not an appropriate comparator, as well as the lack of eculizumab data, an economic comparison with pegcetacoplan was not conducted.

Perspective

B 8. Priority question. The CS base-case includes an “opportunity costs” approach: Kidneys not required by treated patients are reallocated to other patients on the NHS transplant waiting list, producing additional system-level cost savings and QALY gains according to the company.

- a) Please justify the appropriateness of this approach for the reference-case analysis, referencing the NICE Health Technology Evaluation manual (PMG36)(12) and the section on perspective. Explicitly state whether this is proposed as a reference-case or non-reference-case (secondary) analysis.**
- b) Please confirm whether kidney reallocation / opportunity cost adjustments have precedent in previous NICE technology appraisals**

(i.e., provide examples if precedent exists). If not, justify why they are applicable here.

- c) **Provide updated analyses and an updated economic model removing the opportunity cost kidney reallocation assumption and instead including only direct per-patient costs and outcomes (i.e., no reallocation benefits). Report the impact on LYs, QALYs, costs and ICERs.**
- d) **Please, consistent with the NICE manual for non-reference-case analyses, present any benefits/cost-savings from kidney reallocation in a disaggregated format, separately from the reference-case results (i.e., show base-case reference results without reallocation, then present the non-reference reallocation results separately).**
- a) Thank you for the opportunity to respond to this further. The methods we have used to quantify the impact of changes in the demand for organs for transplantation are entirely consistent with NICE's Reference Case. In line with the NICE Health Technology Evaluation Manual (PMG36), which specifies the NHS and Personal Social Services (PSS) perspective, **our opportunity-cost calculations are restricted to NHS cost savings and patient health benefits**

Crucially, the Manual does not limit the reference case to costs and benefits incurred only by patients with the condition under evaluation. It explicitly states that *"for the reference case, the perspective on outcomes should be all relevant health effects, whether for patients or, when relevant, other people (mainly carers)."* Similarly, it notes that NICE's objective is to *"offer guidance that represents an efficient use of available NHS and PSS resources."* Furthermore, it says *"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"*.

Taken together, it follows that potential savings and benefits should not be restricted solely to the C3G/IC-MPGN patient population. Where a new

intervention delivers wider NHS or PSS efficiencies—such as reducing the need for transplants, thereby freeing organ capacity that benefit other patients—these impacts are appropriately included within the reference case.

We also highlight Principle 7 of the principles for developing NICE guidance and standards, which states that recommendations should be based on population benefits and value for money. *“If possible, we consider value for money by calculating the incremental cost-effectiveness ratio (ICER). This is based on an assessment of the intervention’s costs and how much benefit it produces compared with the next best alternative. It is expressed as the ‘cost (in £) per quality-adjusted life year (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.**”* While the term ‘opportunity cost’ in Principle 7 focuses on forgone alternatives, its application in this appraisal—specifically in the context of kidney reallocation—differs; however, the underlying principle remains the same. In both cases, there are potential population health gains, with implications for NHS costs and health outcomes, through the selection of interventions that deliver wider benefits.

The Manual distinguishes non-reference-case analyses primarily where benefits accrue to public bodies outside the NHS and PSS (for example, reduced crime or drug misuse). Because the cost savings modelled here constitute direct reductions in NHS expenditure, they fall within the Reference Case scope. Accordingly, there is no methodological basis to classify this analysis as non-reference case.

These conclusions are supported by independent external experts. Following receipt of this query, the Company consulted three experts in health economics and NICE methodology—Keith Tolley, Professor Mark Sculpher, and Jess Maloney—to obtain external advice (11). Each expert judged that

our opportunity-cost approach, understood as population-health benefits, is compatible with the NICE reference case.

Finally, we note that, during the scope consultation for pegcetacoplan, medical specialties highlighted the benefits associated with fewer patients requiring lifelong kidney replacement therapy, in the form of dialysis or kidney transplantation, and NICE acknowledged in its response that the “*committee will consider any cost-savings associated with delayed/reduced initiation of dialysis*” (NICE, 2025).

- b) Kidney reallocation / opportunity cost adjustments do have precedent in previous NICE technology appraisals, although this appraisal will be setting a new precedent in terms of its overall inclusion.

In TA809 (imlifidase for desensitisation before kidney transplantation), the EAG raised independently from the company—and the committee considered—the opportunity cost to others awaiting a deceased-donor kidney. Recognising Principle 7 and the scarcity of deceased-donor organs, the committee noted that the foregone benefit to an alternative suitable recipient should be taken into account. It ultimately concluded that kidneys are a scarce resource and that decisions should consider opportunity costs alongside equity of access for highly sensitised people.

Looking beyond nephrological conditions, NICE’s guidance for technologies informed by infectious-disease modelling explicitly considers opportunity cost / overall population health. Benefits and costs extend beyond the treated cohort to the wider public through indirect effects (e.g., reduced transmission, herd immunity).

On the basis of these precedents—and consistent with the NICE Manual and NICE’s guiding principles—incorporating organ-allocation opportunity costs in the reference case for this appraisal is justified.

- c) A scenario analysis outlining the model results after excluding the opportunity cost assumption can be found in Table 18.

As identified in responses to B8a and b, the outcomes from these scenarios are considered to exclude critical health benefits of the population and savings that may be accrued across the NHS. However, we provide below the requested information.

Table 18: Model scenario excluding opportunity cost of kidney transplant

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
'New' base case					£35,798	Dominant
Exclusion of cost saved and QALY gain from transplants avoided					£165,388	Dominant

- d) As outlined in our response to B8a, the Company considers that the opportunity cost of kidneys saved forms part of the submission's reference case; accordingly, the benefits and cost savings from kidney reallocation should not be assessed separately in a disaggregated analysis.

We would like to also highlight that several elements of the submission are conservative. In particular, we have not captured potential increases in living (related) donation—and hence the overall kidney pool—that may follow the introduction of a disease-modifying therapy that improves post-transplant longevity. In addition, we have taken a conservative approach by excluding carer disutility from the model. As with people on the transplant waiting list, carers are additional stakeholders who benefit from effective treatments.

Also, it should be noted that the costs used in our opportunity-cost queuing model are derived from NHS data and can be considered robust.

Nonetheless, for completeness, we have provided the requested disaggregated analysis. Disaggregated results were originally provided in the CS Appendix H which provide details as to the QALY and cost savings for the

NHS from pegcetacoplan reducing the need for transplants (“Saved kidney in comparison to SoC”).

These disaggregated data have been updated in Table 19 and Table 20 with the new Company base case following responses to other clarification questions.

Table 19: Summary of aggregated QALY gain in updated Company base case

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

Table 20: Summary of costs by health state in the updated Company base case

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

CKD 3					
CKD 4					
CKD 5					
Transplant					
Haemodialysis					
Peritoneal dialysis					
CV and renal events - Total					
MI					
Acute Stroke					
Post-Stroke					
Heart Failure					
CV - Mortality					
Renal Death					
Saved kidney in comparison to SoC					
Total (discounted)					

Treatment effectiveness

Regression models

B 9. Priority question. Regression model (based on VALIANT) used to estimate uPCR state transitions. Clarification is requested on the structure, implementation, and validation of the regression model used to estimate uPCR state transitions, to ensure the model accurately reflects the trial data and avoids inconsistencies.

- In CS Tables 66 and 67 uPCR is categorised in: uPCR <1.0, uPCR 1.0-3.0 and uPCR >3.0. This is a different categorisation than the model structure (CS Figure 19), i.e. uPCR <1.5, uPCR 1.5-2.0, uPCR 2.0-3.0 and uPCR >3.0 g/g. Please justify how the chosen categorisation (<1.0, 1-3, >3.0) was mapped into the model structure categories (<1.5, 1.5-2.0, 2.0-3.0, >3.0) and whether any reclassification of patients was required.**
- Explain why a multinomial logistic regression (versus alternatives) was selected as the base model (beyond AIC). In particular, justify why a linear regression (for continuous uPCR change), ordered logistic (if**

ordinal states), or multi-state (time-to-event) models were not chosen as base case or explored in scenario analyses. For each alternative model approach, provide a short for rejection/acceptance.

- c) Please provide a comprehensive overview of the regression model presented in CS Table 65 (including full details including the model formula(s) used (including link function), standard errors, z/t-statistics and p-values for all coefficients, covariance matrix of parameter estimate and diagnostics, including assessment of goodness-of-fit assessments (e.g. observed vs predicted transition frequencies by prior-state and time point), calibration plots, residual plots, any tests of proportional odds / parallel lines (if ordered logit used), assessment of multicollinearity) as well as any derived model outputs used in the economic model.
- d) Please explain how the transition probabilities from CS Tables 66 and 67 were calculated from the regression parameters in CS Table 65.
- e) Please provide point estimates and 95%CIs for all transition probabilities presented in CS Table 66. Please also elaborate how the uncertainty related to these transition probabilities is incorporated in the probabilistic analyses.
- f) Please reproduce CS Tables 66 and 67 (separately for SoC and pegcetacoplan), providing the full cell counts (N) based on VALIANT used to estimate each transition (i.e. 'From' represents baseline (week 0) uPCR distribution and 'To' represents the week 26 uPCR distribution).
- g) Please elaborate to what degree CS Tables 66 and 67 are consistent with the VALIANT trial data.
- h) Please provide evidence indicating that indeed the transition probabilities from CS Tables 66 and 67 are consistent with the modelling at week 26 (SoC) and week 52 (pegcetacoplan).

- i) **The CS states placebo data beyond 26 weeks were excluded while pegcetacoplan arm used all 52 weeks. This asymmetry may bias treatment effect estimates. Please provide comprehensive details for CS scenario 1, using only the randomised period (weeks 0–26) for both arms (i.e. identical time horizon for each arm). This should include re-estimation of the chosen regression model (including full details including the model formula(s) used (including link function), standard errors, z/t-statistics and p-values for all coefficients, covariance matrix of parameter estimate and diagnostics, including assessment of goodness-of-fit assessments (e.g. observed vs predicted transition frequencies by prior-state and time point), calibration plots, residual plots, any tests of proportional odds / parallel lines (if ordered logit used), assessment of multicollinearity), providing point estimates and 95%CIs for all transition probabilities and any derived model outputs used in the economic model.**
- a) Thank you for bringing this to our attention. This misunderstanding appears to have been caused by typos in the model schematic in the original CS and model. In these figures it was indicated that the model used four UPCR sub-groups defined as:
- i. <1.5g/g
 - ii. 1.5g/g-2.0g/g
 - iii. 2.0g/g-3.0g/g
 - iv. >3.0g/g

As highlighted in the updated model schematic in response to B4, the correct UPCR sub-group thresholds used in the model, and for which data from VALIANT were analysed, are:

- i. <1.0g/g
- ii. 1.0g/g-3.0g/g
- iii. >3.0g/g

Following the identification of the error in the model schematic, it is confirmed that no mapping or reclassification of patients were required to incorporate data into the model.

b) Regarding the use of a linear model with continuous UPCR:

Such an approach would require strong assumptions about the trajectory of UPCR over time, as well as the functional form of its relationships with eGFR, health utilities, and costs. EAG also questioned the linearity of the relationship between UPCR and eGFR. In contrast, the approach used in this analysis does not rely on these assumptions. Moreover, the use of discrete health states is a standard and widely accepted method in cost-effectiveness modelling.

Regarding multi-state models:

Our understanding is that multi-state (time-to-event) models are most advantageous when transitions between health states are observed in continuous time and the exact timing of events is available. In our study, UPCR measurements were collected only at discrete follow-up visits. As such, a discrete-time framework was deemed more appropriate given the structure of the data.

Regarding multinomial logistic regression and ordered logistic regression

Both multinomial logistic regression and ordered logistic regression were explored for modelling transitions between UPCR-based health states. The final model choice was primarily guided by the AIC, with the multinomial logistic regression providing a better fit. This model offers greater flexibility and is more broadly applicable, particularly when the assumption of proportional odds may not hold or when capturing more complex relationships between predictors and outcome categories.

However, given the inherently ordered nature of the UPCR health states, the ordered logistic regression model also represents a theoretically appropriate alternative (Table 21). To assess the impact of this modelling choice on the cost-effectiveness analysis, we have also calculated the transition probabilities using the best-fitting ordered logistic model (Table 22). This allows us to conduct a sensitivity analysis and evaluate the robustness of the cost-effectiveness results to the choice of regression model.

It is worth noting that the transition probabilities from ordered logistic model are very similar to the ones used in the CS.

Table 21: Best-fitting ordered logistic regression outcomes

	Estimate	Std. Error	t value	P-value
fromHS 2	██████	0.306	7.425	<0.01
fromHS 3	██████	0.421	12.169	<0.01
ARMPlacebo	██████	0.250	4.492	<0.01
HS 1 HS 2	██████	0.260	7.180	<0.01
HS 2 HS 3	██████	0.368	13.460	<0.01
AIC	516.72			

Table 22: Calculated transition probabilities from the best-fitting ordered logistic regression analysis

From\To	Pegcetacoplan		
	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	██████	██████	██████
uPCR 1.0 - 3.0 g/g	██████	██████	██████
uPCR >3 g/g	██████	██████	██████
From\To	SoC		
	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	██████	██████	██████
uPCR 1.0 - 3.0 g/g	██████	██████	██████
uPCR >3 g/g	██████	██████	██████

A summary of the impact on model outcomes when using the ordered logistic regression are summarised in

Table 23: Scenario analysis - ordered logistic model outcomes to inform UPCR transitions

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
'New' base case	██████	██████ 	██████	██████	£35,798	Dominant
Ordered logistic model outcomes to inform UPCR transitions	██████	██████ 	██████	██████	£42,681	Dominant

- c) Below, we provide all the requested parameters describing the regression model presented in CS Table 65, which we believe are consistent with the applied methods. The model formula used to calculate the transition probabilities is detailed in the response to Question B9c, while the observed versus predicted transition frequencies are discussed in the response to Question B9f.

Table 24: Parameters of multinomial logit model

Covariant	Health state	Estimate	Standard error	Z-statistic	P-value
Intercept	HS2	████	0.27	-7.12	<0.01
	HS3	████	100.17	-0.14	0.89
HS2 at previous visit	HS2	████	0.32	7.14	<0.01
	HS3	████	100.17	0.12	0.90
HS3 at previous visit	HS2	████	0.50	4.93	<0.01
	HS3	████	100.17	0.16	0.88
No APL-2 Arm	HS2	████	0.33	4.29	<0.01
	HS3	████	0.47	4.04	<0.01
AIC	513.30				

Table 25: Covariance matrix

	To HS 2 – Intercept	To HS 2 - HS2 at previous visit	To HS 2 - HS3 at previous visit	To HS 2 - No APL-2 Arm	To HS 3 – Intercept	To HS 3 - HS2 at previous visit	To HS 3 - HS3 at previous visit	To HS 3 - No APL-2 Arm
To HS 2 – Intercept	0.0730	-0.0659	-0.0687	-0.0270	0.0221	-0.0174	-0.0196	-0.0220
To HS 2 - HS2 at previous visit	-0.0659	0.1003	0.0668	-0.0016	-0.0168	0.0400	0.0161	0.0028
To HS 2 - HS3 at previous visit	-0.0687	0.0668	0.2521	0.0096	-0.0287	0.0122	0.1517	0.0333
To HS 2 - No APL-2 Arm	-0.0270	-0.0016	0.0096	0.1086	-0.0266	0.0079	0.0165	0.0884

To HS 3 - Intercept	0.0221	-0.0168	-0.0287	-0.0266	10034.2700	10034.2300	10034.2500	-0.0847
To HS 3 - HS2 at previous visit	-0.0174	0.0400	0.0122	0.0079	10034.2300	10034.3400	10034.2300	-0.0164
To HS 3 - HS3 at previous visit	-0.0196	0.0161	0.1517	0.0165	10034.2500	10034.2300	10034.3900	0.0450
To HS 3 - No APL-2 Arm	-0.0220	0.0028	0.0333	0.0884	-0.0847	-0.0164	0.0450	0.2194

Table 26: Confusion matrix

Confusion matrix			
	Reference HS1	Reference HS2	Reference HS3
Prediction: HS1	99	19	0
	46	104	14
Prediction: HS2	8	19	56
Statistics			
Accuracy (95% CI)	0.7096 (0.6601, 0.7557)		
No Information Rate	0.4192		
P-Value	< 0.01		
Statistics by HS			
	HS1	HS2	HS3
Sensitivity	0.6470588	0.7323944	0.8
Specificity	0.9103774	0.7309417	0.9084746
Positive Prediction Value	0.8389831	0.6341463	0.6746988
Negative Prediction Value	0.7813765	0.8109453	0.9503546
Precision	0.8389831	0.6341463	0.6746988

- d) Transition probabilities from CS Tables 66 and 67 were calculated from the regression parameters in CS Table 65 using the following equation:

$$Value_{HS(i)} = \exp(\text{Intercept} + \sum_{k=1}^n (\text{Covariate}_k * \text{Parameter Value}_k))$$

Where

$Value_{HS}$ are values used to calculate final probabilities for HS(i)

$Covariate_k$ is a regression parameter

$Parameter\ Value_k$ is the value of parameter (in case of presented regression model all of them are binary variables, e.g. if patient was from No APL-2 Arm then Parameter Value is equal 1, and 0 otherwise).

Probabilities of movement to HS(i) are then calculated as:

$$Prob_{HS(i)} = \frac{Value_{HS(i)}}{1 + \sum_{k=2}^3 Value_{HS(k)}}$$

For HS2 and HS3. HS1 is calculated as complement of sum of probabilities of movement to HS2 and HS3.

- e) The transition probabilities have now been incorporated into the updated probabilistic analyses using a Dirichlet distribution, based on mean values and standard errors derived via a bootstrapping method. In the bootstrapping process, transition probabilities were generated from the coefficients of a multinomial regression model and their corresponding standard errors, assuming a normal distribution. The sample SD for each transition probability was calculated, and the standard error SE was derived from the SD, accounting for the number of patients in the trial (61 for SoC and 63 for PEG). The results for SE for each transitions used in the model are presented below.

Table 27: UPCR transition - SEs derived using bootstrapping method

From\To	SEpegcetacoplan		
	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	5.41%	0.86%	6.22%
uPCR 1.0 - 3.0 g/g	2.75%	3.76%	6.26%
uPCR >3 g/g	2.59%	4.09%	6.27%
From\To	SESoC		
	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	4.03%	2.56%	6.32%
uPCR 1.0 - 3.0 g/g	1.20%	5.39%	6.36%
uPCR >3 g/g	1.14%	5.52%	6.37%

f) Transitions rates by HS for pegcetacoplan

Table 28: Transitions rates by HS for pegcetacoplan

Transition		HS 1 ↓ HS 1	HS 1 ↓ HS 2	HS 1 ↓ HS 3	HS 2 ↓ HS 1	HS 2 ↓ HS 2	HS 2 ↓ HS 3	HS 3 ↓ HS 1	HS 3 ↓ HS 2	HS 3 ↓ HS 3
Baseline -> Week 26	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■
Week 26 -> Week 52	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■

Table 29: Transitions rates by HS for SoC

Transition		HS 1 ↓ HS 1	HS 1 ↓ HS 2	HS 1 ↓ HS 3	HS 2 ↓ HS 1	HS 2 ↓ HS 2	HS 2 ↓ HS 3	HS 3 ↓ HS 1	HS 3 ↓ HS 2	HS 3 ↓ HS 3
Baseline -> Week 26	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■

g) UPCR transitions presented in CS Tables 66 and 67 are derived based on the VALIANT trial data with the use of widely accepted statistical methods. To better show the consistency of the model results with the actual data we have generated raw transition matrices.

Table 30: Transitions rates by HS for pegcetacoplan

Transition	HS 1 ↓ HS 1	HS 1 ↓ HS 2	HS 1 ↓ HS 3	HS 2 ↓ HS 1	HS 2 ↓ HS 2	HS 2 ↓ HS 3	HS 3 ↓ HS 1	HS 3 ↓ HS 2	HS 3 ↓ HS 3

Cycle 1	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■
Cycle 2	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■
Cycle 3	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■
Cycle 4	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■

HS, health state; N, number

Based on the above, we have calculated the average transition matrix, taking into account the number of subjects and transitions across four cycles. The results are presented in the table below and compared with Table 67 from the CS.

Table 31: uPCR transitions with pegcetacoplan

From\To	Table 67 from CS			Based on raw matrices		
	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	■	■	■	■	■	■
uPCR 1.0 - 3.0 g/g	■	■	■	■	■	■
uPCR >3 g/g	■	■	■	■	■	■

The same exercise has been performed for SoC, for which observations from only 2 cycles are available and compared with Table 66 from the CS. The results indicate close alignment between CS Tables 66 and 67 and the VALIANT trial data.

Table 32: Transitions rates by HS for SoC

Transition		HS 1 ↓ HS 1	HS 1 ↓ HS 2	HS 1 ↓ HS 3	HS 2 ↓ HS 1	HS 2 ↓ HS 2	HS 2 ↓ HS 3	HS 3 ↓ HS 1	HS 3 ↓ HS 2	HS 3 ↓ HS 3
Cycle 1	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■
Cycle 2	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■

Table 33: uPCR transitions with SoC

	Table 66 from CS			Based on raw matrices		
From\To	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	■	■	■	■	■	■
uPCR 1.0 - 3.0 g/g	■	■	■	■	■	■
uPCR >3 g/g	■	■	■	■	■	■

- h) See response above (B9f) and the comparison between probabilities from CS Tables 66 and 67 and VALLIANT data.
- i) Below, we provide all the requested parameters describing the regression model used in CS scenario 1, which we believe are consistent with the applied methods. The model formula used to calculate the transition probabilities is detailed in the response to Question B9c, while the observed

versus predicted transition frequencies are discussed in the response to Question B9e.

Table 34: Parameters of multinomial logit model

Covariant	Health state*	Estimate	Standard error	Z-statistic	P-value
Intercept	HS2	████	0.40	-4.95	<0.01
	HS3	████	80.73	-0.18	0.86
HS2 at previous visit	HS2	████	0.42	4.89	<0.01
	HS3	████	80.73	0.13	0.89
HS3 at previous visit	HS2	████	0.58	4.18	<0.01
	HS3	████	80.73	0.18	0.85
No APL-2 Arm	HS2	████	0.36	4.44	<0.01
	HS3	████	0.60	5.02	<0.01
AIC	513.30				

Table 35: Covariance matrix

	To HS 2 - Intercept	To HS 2 - HS2 at previous visit	To HS 2 - HS3 at previous visit	To HS 2 - No APL-2 Arm	To HS 3 - Intercept	To HS 3 - HS2 at previous visit	To HS 3 - HS3 at previous visit	To HS 3 - No APL-2 Arm
To HS 2 - Intercept	0.1608	-0.1353	-0.1527	- 0.065 6	0.0822	-0.0627	-0.0780	- 0.054 2
To HS 2 - HS2 at previous visit	-0.1353	0.1766	0.1341	0.014 2	-0.0573	0.0879	0.0556	0.014 9
To HS 2 - HS3 at previous visit	-0.1527	0.1341	0.3412	0.049 3	-0.1101	0.0582	0.2301	0.083 6
To HS 2 - No APL-2 Arm	-0.0656	0.0142	0.0493	0.132 2	-0.0712	0.0318	0.0625	0.109 3
To HS 3 - Intercept	0.0822	-0.0573	-0.1101	- 0.071 2	6517.925 0	- 6517.708 0	- 6517.862 0	- 0.284 7
To HS 3 - HS2 at previous visit	-0.0627	0.0879	0.0582	0.031 8	- 6517.708 0	6517.870 0	6517.707 0	0.022 4

To HS 3 - HS3 at previous visit	-0.0780	0.0556	0.2301	0.062 5	- 6517.862 0	6517.707 0	6517.988 0	0.209 4
To HS 3 - No APL-2 Arm	-0.0542	0.0149	0.0836	0.109 3	-0.2847	0.0224	0.2094	0.355 3

Table 36: Confusion matrix

Confusion matrix			
	Reference HS1	Reference HS2	Reference HS3
Prediction: HS1	42	11	0
	35	80	8
Prediction: HS2	8	17	43
Statistics			
Accuracy (95% CI)	0.6762 (0.6136, 0.7345)		
No Information Rate	0.4426		
P-Value	< 0.01		
Statistics by HS			
	HS1	HS2	HS3
Sensitivity	0.4941176	0.7407407	0.8431373
Specificity	0.9308176	0.6838235	0.8704663
Positive Prediction Value	0.7924528	0.6504065	0.6323529
Negative Prediction Value	0.7748691	0.768595	0.9545455
Precision	0.7924528	0.6504065	0.6323529

B 10. Priority question. Regression model (based on VALIANT) used to estimate CKD state transitions. Details are requested on the CKD regression model, including assumptions of linearity and treatment effects, to assess whether the model appropriately predicts eGFR decline and CKD progression.

- a) In CS Tables 71 and 73, uPCR is categorised in: uPCR <1.0, uPCR 1.0-3.0 and uPCR >3.0. This is a different categorisation than the model structure (CS Figure 19), i.e. uPCR <1.5, uPCR 1.5-2.0, uPCR 2.0-3.0 and uPCR >3.0 g/g. Please justify how the chosen categorisation (<1.0, 1-3,

>3.0) was mapped into the model structure categories (<1.5, 1.5-2.0, 2.0-3.0, >3.0) and whether any reclassification of patients was required.

- b) Explain why a linear regression (rather than non-linear, spline, or piecewise models) was used to estimate CKD state transitions. Moreover, justify, with supporting evidence, why the relation between eGFR decline and uPCR was assumed to be linear? Provide exploratory plots (scatter + loess/spline) of eGFR change vs uPCR change and show whether linearity is reasonable.**
- c) Please provide a comprehensive overview of the regression model presented in CS Table 70 (including full details including the model formula(s) used (including link function), standard errors, z/t-statistics and p-values for all coefficients, covariance matrix of parameter estimate and diagnostics, including assessment of goodness-of-fit assessments (e.g. observed vs predicted eGFR decline), residual plots, assessment of multicollinearity) as well as any derived model outputs used in the economic model.**
- d) Provide observed mean (and SD) eGFR values and eGFR change by uPCR subgroup and treatment arm at each visit in VALIANT. Overlay predicted values from the linear model to permit visual assessment of fit.**
- e) Provide the mathematical steps and worked example used to convert the regression model (CS Table 70) via the eGFR decline estimates (CS Table 71) into the per-cycle CKD transition probabilities reported in CS Table 73. Explicitly state any assumptions (e.g. within-cycle linear decline, rounding, distributional assumptions).**
- f) Please elaborate to what degree CS Table 73 is consistent with the VALIANT trial data.**
- g) Please justify why the treatment covariate was included in the regression model (i.e. what causal or statistical role does treatment play beyond via uPCR). Provide empirical evidence that CKD stage**

transitions should be treatment-dependent beyond the effect mediated by uPCR (i.e. why would two patients with identical uPCR have different eGFR trajectories by treatment arm?).

h) Please provide scenario analyses (as well as an updated economic model) using a regression model (based on VALIANT) to estimate CKD state transitions excluding the treatment covariate.

- a) Please see our response to B9a in order to address this question.
- b) To clarify, the model did not assume a linear relationship between eGFR decline and uPCR; therefore, no explanatory plots illustrating such a relationship can be provided. However, a linear slope for eGFR decline was assumed, differentiated according to uPCR level, which fell into one of three predefined categories. Modelling CKD progression using a constant eGFR slope is a well-established and commonly used approach in health economic evaluations, and eGFR slopes are also routinely used by clinicians in clinical practice to monitor disease progression. This methodology has also been applied in other economic models, including those reviewed in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy).

Our model extended this standard approach by incorporating the assumption that the rate of eGFR decline depends on uPCR level. The company submission cited multiple sources supporting this assumption, demonstrating that CKD progression varies with the degree of proteinuria. This was further confirmed by statistical analysis of trial data, which showed distinct eGFR slopes across the three uPCR categories, based on uPCR values and treatment received.

- c) Below, we provide all the requested parameters describing the regression model used in CS Table 70, which we believe are consistent with the applied methods. Observed changes in eGFR are presented in the response to Question B10d.

Table 37: Regression model results

	Estimate	Std. Error	t value	Pr(> t)

(Intercept)	████	1.098	0.791	0.430
ARMPlacebo	████	1.592	-1.469	0.143
Health_stateHS 2	████	1.638	-0.963	0.336
Health_stateHS 3	████	2.011	-1.604	0.109
Spearman correlation between ARM and Health_state				0.3425179

Table 38: Covariance matrix

	(Intercept)	ARMPlacebo	Health_stateHS 2	Health_stateHS 3
(Intercept)	1.2046	-0.3312	-1.0530	-1.0390
ARMPlacebo	-0.3312	2.5336	-0.8285	-0.9356
Health_stateHS 2	-1.0530	-0.8285	2.6836	1.4673
Health_stateHS 3	-1.0390	-0.9356	1.4673	4.0452

Figure 3: Residuals plot, by arm

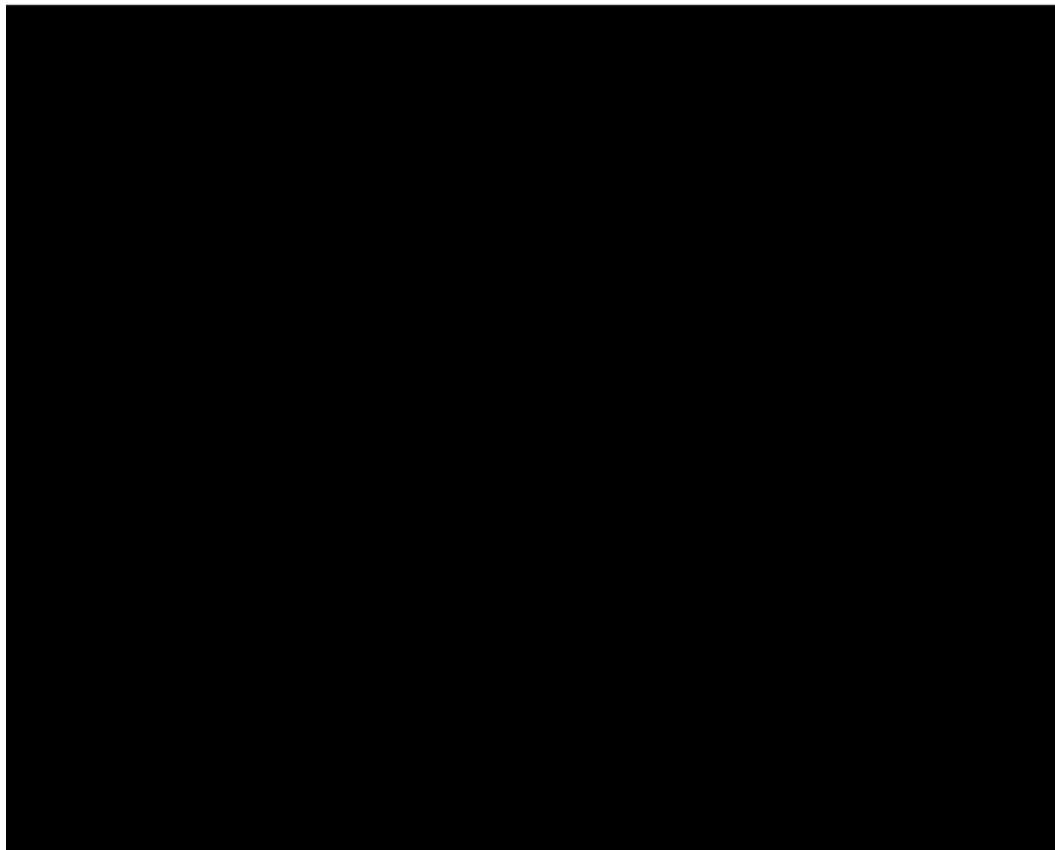


Figure 4: Residuals plot for health state

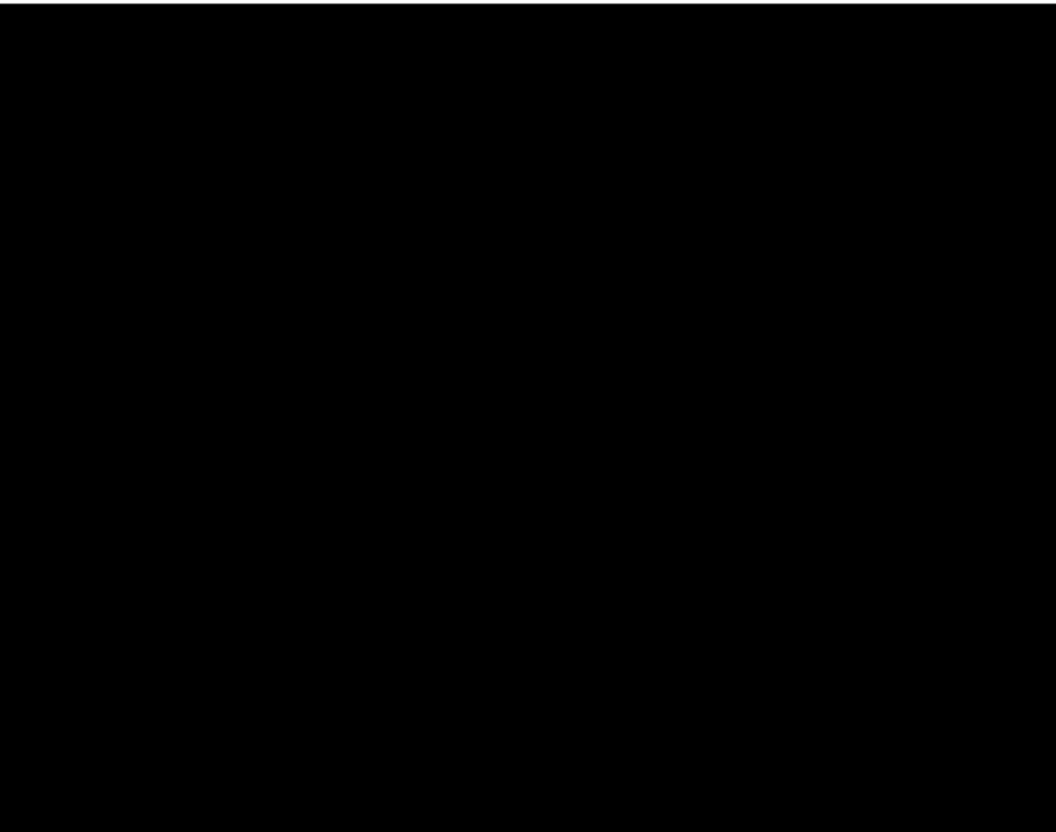


Table 39: Derived eGFR decline every 12 weeks

	Pegcetacoplan	SoC
HS 1		
HS 2		
HS 3		

d)

Table 40: Mean eGFR – pegcetacoplan

Timepoint	HS1			HS2			HS3		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Baseline		26.2	11.7		35.9	6.2		29.3	6.0
Week 4		33.0	8.0		38.3	7.1		26.6	6.7
Week 8		36.7	6.7		38.0	9.2		21.5	5.5
Week 12		35.9	6.3		36.1	8.1		17.7	5.6
Week 16		35.5	6.2		34.4	7.7		17.8	5.9
Week 20		32.0	5.8		38.4	7.8		24.2	8.6
Week 24		36.1	6.3		39.1	8.1		18.3	7.5

Figure 5: Mean eGFR from VALIANT over time, by UPCR sub-group - SOC

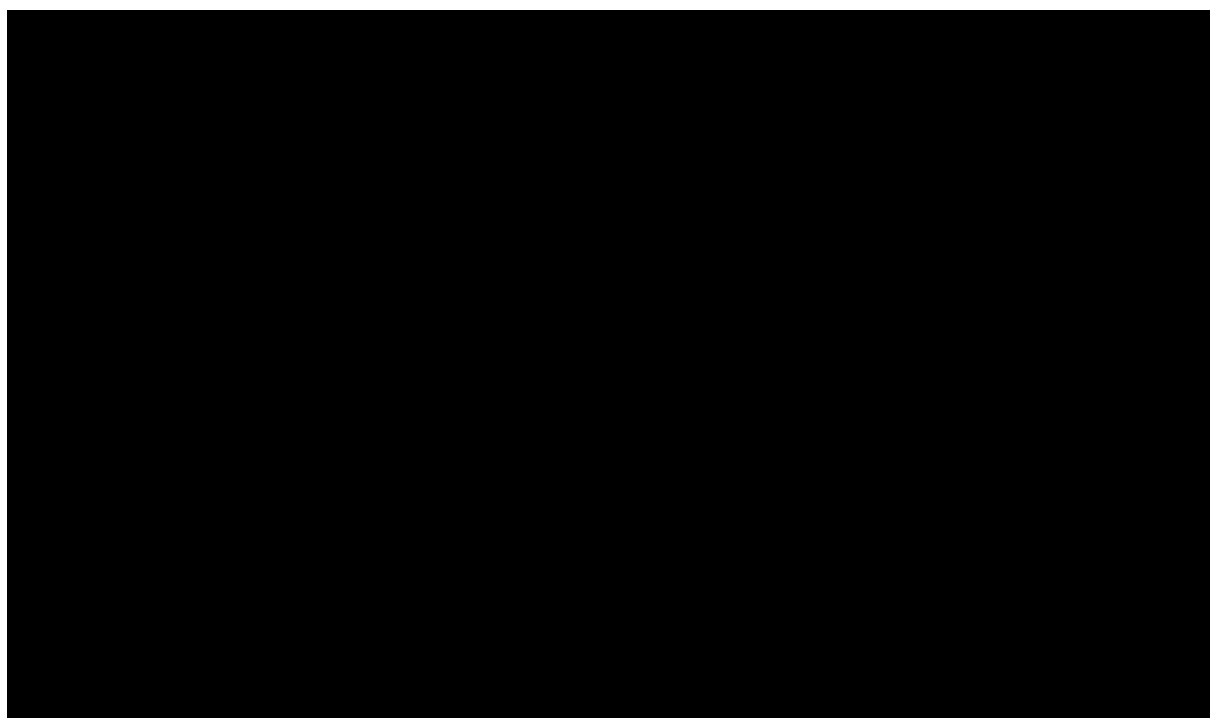


Table 43: eGFR change from previous visit – pegcetacoplan

Timepoint	HS1			HS2			HS3		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Baseline	■	0	0	■	0	0	■	0	0
Week 4	■	12.004	2.911	■	15.543	2.886	■	14.711	3.678
Week 8	■	13.893	2.536	■	12.671	3.073	■	8.365	2.160
Week 12	■	11.978	2.117	■	11.767	2.631	■	11.870	3.754
Week 16	■	11.868	2.066	■	15.298	3.421	■	8.969	2.990
Week 20	■	12.743	2.327	■	7.765	1.585	■	12.048	4.259
Week 24	■	10.059	1.751	■	11.943	2.490	■	12.160	4.964
Week 26	■	12.570	2.258	■	8.641	1.802	■	8.036	2.841
Week 28	■	9.868	1.668	■	12.608	3.058	■	9.506	3.169
Week 32	■	22.293	3.941	■	7.757	1.779	■	6.877	2.175
Week 36	■	14.957	2.644	■	9.324	2.085	■	5.426	1.809
Week 42	■	16.223	2.914	■	4.955	1.108	■	3.084	0.975
Week 48	■	12.646	2.108	■	10.432	2.788	■	10.080	3.188
Week 52	■	12.300	2.209	■	8.846	2.029	■	5.481	1.733

Figure 6: Mean eGFR change from VALIANT over time, by UPCR sub-group - pegcetacoplan

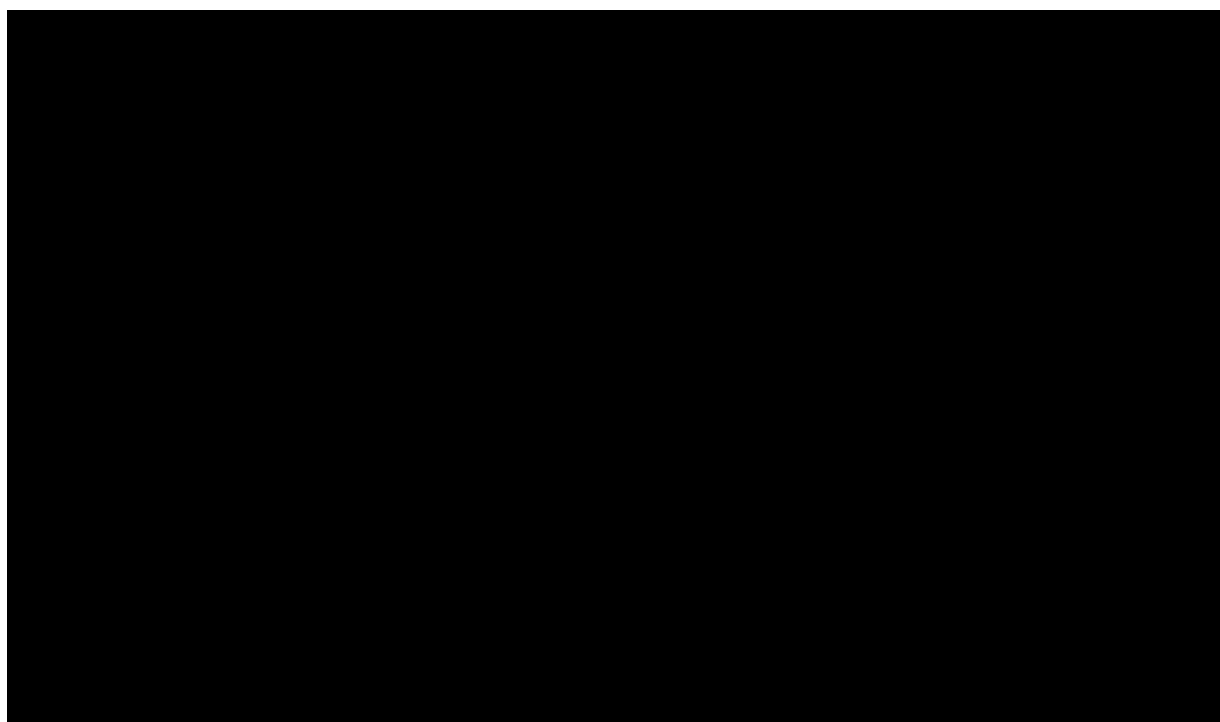


Table 44: eGFR change from previous visit – SoC

Timepoint	HS1			HS2			HS3		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Baseline	■	0	0	■	0	0	■	0	0
Week 4	■	12.004	2.911	■	15.543	2.886	■	14.711	3.678
Week 8	■	13.893	2.536	■	12.671	3.073	■	8.365	2.160
Week 12	■	11.978	2.117	■	11.767	2.631	■	11.870	3.754
Week 16	■	11.868	2.066	■	15.298	3.421	■	8.969	2.990
Week 20	■	12.743	2.327	■	7.765	1.585	■	12.048	4.259
Week 24	■	10.059	1.751	■	11.943	2.490	■	12.160	4.964
Week 26	■	12.570	2.258	■	8.641	1.802	■	8.036	2.841

Figure 7: Mean eGFR change from VALIANT over time, by UPCR sub-group - SOC

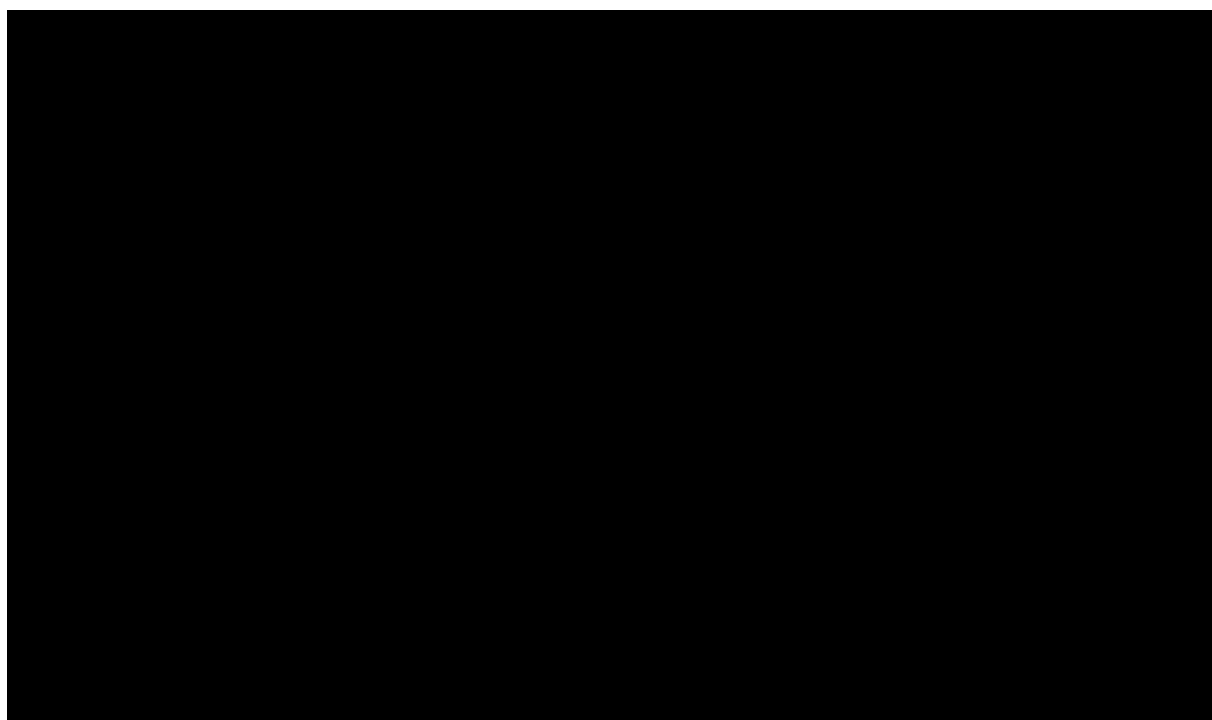


Figure 8: Comparison with regression model – pegcetacoplan

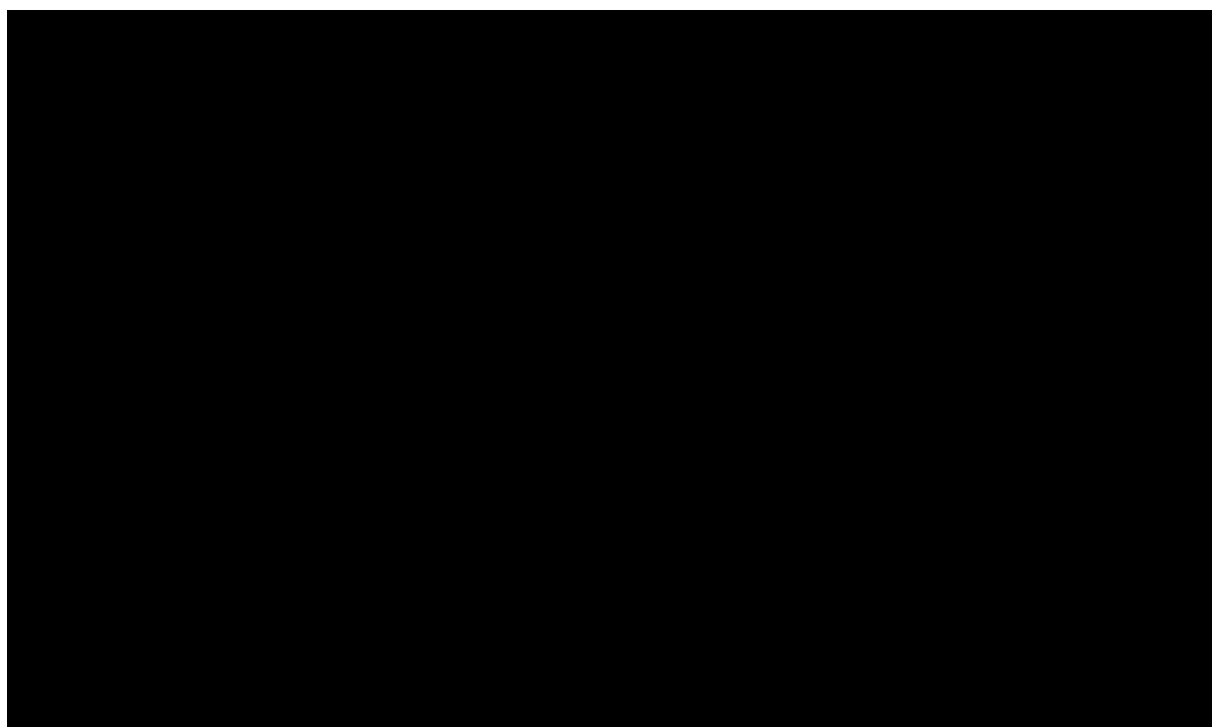
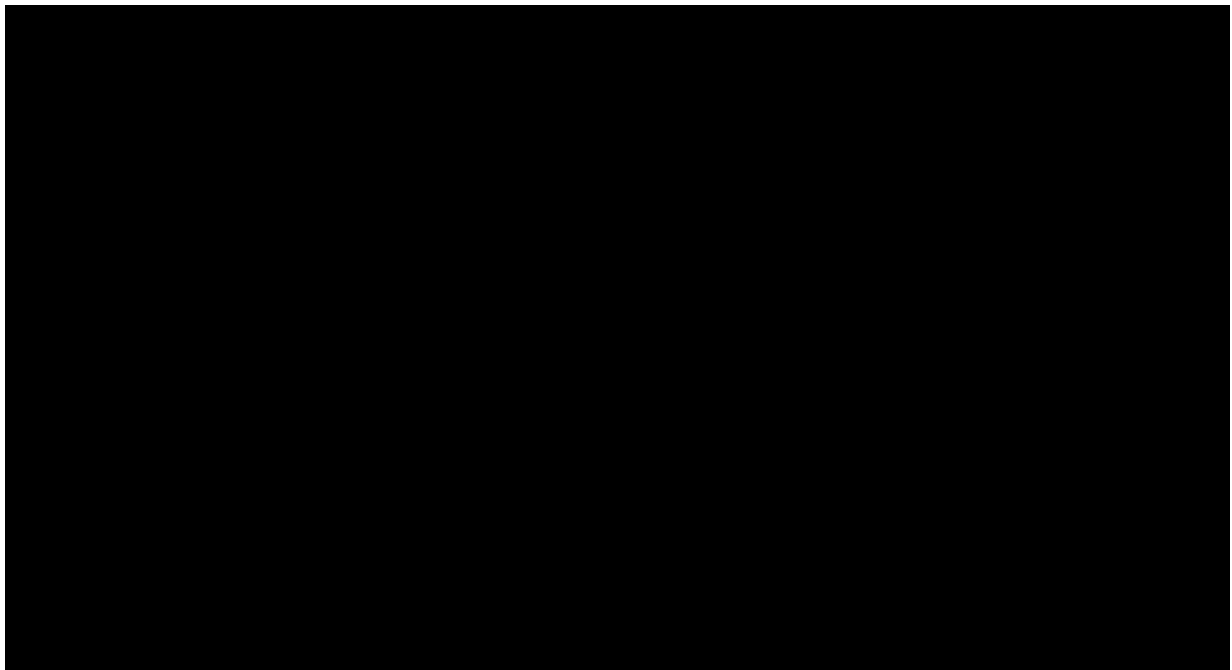


Figure 9: Comparison with regression model – SoC



eGFR values presented in the above graphs were calculated using linear regression based on baseline eGFR values within specific health states (uPCR subgroups).

However, it is important to note that this comparison may not fully reflect the actual modelled eGFR values for several reasons:

- In the cost-effectiveness model, patients transition between health states over time. Therefore, the mean baseline value within a specific health state does not necessarily represent the baseline eGFR of patients in that state at a particular time point (e.g., Week 12).
 - eGFR values were assigned based on the patient's health state at each specific visit, which may vary over time. Consequently, a single patient's eGFR data may contribute to multiple health states across the study duration.
- e) Average time to CKD stage change was calculated based on length of the eGFR ranges defining CKD stages (i.e. as CKD 2 spans from eGFR equal to 60 mL/min to 89 mL/min, length of CKD 2 stage is 30, due to average eGFR in CKD 1 stage at baseline in VALIANT trial being [REDACTED], it was assumed that CKD 1 will have length of 31) and eGFR decline in specific states:

Table 45: Defined range of eGFR values used in each CKD health state

	Definition (eGFR values)	Length
CKD 1	≥90	31
CKD 2	60-89	30
CKD 3	30-59	30
CKD 4	15-29	15
CKD 5	<15	15

Table 46: eGFR drop per cycle in model

	Pegcetacoplan	SoC
HS 1	■	■
HS 2	■	■
HS 3	■	■

I.e. average time to move from CKD stage 2 to CKD stage 3 for pegcetacoplan in HS 2 is: ■ cycles.

Probability of moving between CKD stages is calculated as 1/(average time to move between CKD stages). Therefore, based on the above example, per cycle probability of moving from CKD 2 to CKD 3 for a patient receiving pegcetacoplan in HS 2 is: ■.

- f) The probability of transitioning to the subsequent CKD stage, based on eGFR, was calculated using the approach described in the response to Question B10e. This method relies on eGFR slopes estimated directly from the VALIANT trial data. The fit of these estimated slopes to the observed trial data is detailed in the response to Question B10d.

Accordingly, CS Table 73 aligns with the trial data, with the caveat that not all transitions were sufficiently represented in the trial. Therefore, some values are based on extrapolations from the assumed eGFR slope.

As previously outlined in the response to Question B9, modelling CKD progression using a constant eGFR slope is a well-established and widely accepted approach in health economic evaluations. eGFR slopes are also

routinely used in clinical practice to monitor disease progression. This methodology has been employed in other economic models, including those reviewed as part of GID-TA11331 (iptacopan for treating complement 3 glomerulopathy).

- g) It is agreed, in principle, patients with identical uPCR levels should not exhibit different eGFR trajectories solely based on treatment arm. However, it is possible that treatment has an additional effect on eGFR beyond its impact on uPCR improvement. While this effect was not measured in the VALIANT trial in a way that would allow for its inclusion in the economic model, it cannot be entirely ruled out.

Our rationale for including treatment as a covariate in the regression was based on the observation that, even within the same uPCR category, actual values and improvements in terms of the uPCR differ between treatment arms. The uPCR health states used in the model, based on predefined cut-offs, are clinically supported but represent a balance between model complexity, clarity, and the limitations of the available data. Therefore, instead of increasing the number of uPCR health states, we included treatment as a covariate to account for these differences.

Importantly, the treatment effect is not limited to shifting patients into lower uPCR categories; it also appears to reduce uPCR levels to varying degrees among patients who remain within the same category. This more nuanced effect is not fully captured by the categorical uPCR states alone, which further supports the inclusion of the treatment covariate in the model.

The table below compares the average change in uPCR levels between treatment arms for patients within each uPCR category at Week 26. As shown, pegcetacoplan demonstrates an improvement in uPCR levels even within higher uPCR categories. In contrast, patients receiving SoC not only show a smaller improvement in the lowest uPCR category, but also exhibit an increase in uPCR levels within both groups >1 g/g.

Given these differences in achieved uPCR reductions, it is considered reasonable to assume differential eGFR decline between treatment arms.

Table 47: Average change from baseline in uPCR at 26 weeks, by category and treatment arm

uPCR category	Pegcetacoplan	SoC
uPCR <1.0 g/g	██████████	██████████
uPCR 1.0 - 3.0 g/g	██████████	██████████
uPCR >3 g/g	██████████	██████████

h)

Table 48: Regression model results

	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	██████████	1.079	0.521	0.603
Health_stateHS 2	██████████	1.556	-1.506	0.133
Health_stateHS 3	██████████	1.927	-2.123	0.034

The model outcomes in Table 48 translate to eGFR decline outlined in Table 49 - keeping the assumption of no increase in eGFR possible in HS.

Table 49: Alternative eGFR decline, by UPCR sub-group

	eGFR decline per 12 weeks
HS 1	██████████
HS 2	██████████
HS 3	██████████

Table 50 illustrates the impact on the model when excluding the treatment covariate from the eGFR decline regression analysis. However, as outlined in response to B10g, it is considered inappropriate to exclude a treatment covariate in the eGFR regression analysis due to the outcomes not fully captured when looking at eGFR decline by UPCR sub-groups alone.

Table 50: Scenario analysis – eGFR regression model excluding the treatment covariate

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
'New' base case	██████████	██████████	██████████	██████████	£35,798	Dominant
Exclusion of	██████████	██████████	██████████	██████████	£100,606	Dominant

B 11. Priority question. The use of two regression models. Justification is requested for the use of two linked regression models and clarification of how double-counting is avoided, to evaluate whether a more parsimonious modelling approach could be appropriate.

- a) Currently two regression models are combined: CS Table 65 (multinomial logistic regression for uPCR state transitions) and CS Table 70 (linear model for eGFR decline with uPCR covariate). Please justify why two linked regressions were used rather than a parsimonious single model that could simultaneously capture uPCR and eGFR (e.g. a multinomial logistic regression for uPCR state transitions with eGFR decline as covariate).**
 - b) Two separate regression models, especially with both including a treatment covariate, risks double-counting. Please justify and clarify how double-counting is avoided.**
 - c) Please provide scenario analyses (as well as an updated economic model) using one combined regression model to inform the transition probabilities based on the VALIANT trial data.**
- a) Thank you for this query. A separate linear model for eGFR decline with the uPCR covariate was used due to the low number of transitions between different CKD stages observed in the clinical trial. Although a treatment-induced change in uPCR was observed almost immediately after treatment initiation, assessing its impact on CKD stage transitions would require a longer follow-up period and a larger sample size.

This issue was particularly relevant for transitions to more advanced CKD stages, as patients in the VALLIANT trial had relatively high baseline eGFR values. Specifically, only 3.23% of patients entered the study in CKD stage 4.

As shown in the response to Question B10e, the average time to progress from CKD stage 2 to stage 3, based on the assumed eGFR slope, exceeds 42 model cycles (i.e. 126 months), while the randomized phase of the trial had a follow-up of only 26 months.

Given these limitations, modelling CKD progression based on eGFR slope remains appropriate, as it aligns with clinical practice where eGFR decline is routinely used to assess prognosis. As previously discussed in the response to Question B9, the use of a constant eGFR slope to model CKD progression is a well-established and widely accepted approach in health economic evaluations. This methodology has been used in other economic models, including those reviewed under GID-TA11331 (iptacopan for treating complement 3 glomerulopathy).

- b) Double-counting is explicitly avoided by adjusting the linear model for eGFR decline based on the uPCR category, which is estimated using a multinomial logistic regression model for uPCR state transitions.
- c) As already outlined in response to B11a, using one combined regression model to inform the transition probabilities is not feasible due to the limited follow-up of the trial and the considered sample size of patients, which resulted in too few or no observed transitions between specific CKD stages, which mostly concerns more advanced stages.

B 12. Priority question. Converting the regression models to cycle transition probabilities. Details are requested on the methodology used to convert trial-derived transition probabilities for use in the economic model, to ensure transparency and reproducibility of the modelled results.

- a) **Please provide exact method, formula and worked example used to combine the transition probabilities provided in CS Tables 66 and 67 with the transition probabilities derived from the regression model presented in CS Table 71, to obtain the transition probabilities used in the economic model. Please also provide the resulting transition matrix (point estimates and 95%CIs for all transition probabilities).**

- b) Provide the exact method, formula and worked example used to convert trial-derived transition probabilities (i.e. over 52 and 26 weeks) into the per-cycle (12 week) transition probabilities in CS Table 73. If any correction or adjustment was applied, state the reference and show a worked calculation. Please also see for instance the methods described in Chhatwal (2016)(13) Gidwani (2020)().**
- c) The company suggested that assessing long-term, durable changes (instead of focusing on short-term changes) from baseline is preferred for examining clinical effectiveness. For informing cost-effectiveness modelling, these assessments can hide transient but clinically relevant changes (e.g. temporary worsening or improvement) that may influence long-term extrapolation. It is fundamental to examine potential mechanisms that are apparent in the data. The current approach seems to ignore variation/granularity over time (transitions within this time period, potentially to an intermediate state). Please elaborate on the implications of the current approach.**

Please also reproduce CS Tables 66 and 67 (separately for SoC and pegcetacoplan), providing the full cell counts (N) based on VALIANT used to estimate each transition per time point comparing it with the subsequent time point.

- a)** Thank you for the opportunity to further describe this methodology. Probabilities for both transitions between uPCR states and CKD stages are based on the uPCR stage the patient is in at the time. This can be interpreted as the CKD stage transition being considered first (i.e. the patient either remains in the same stage or progresses to the next CKD stage), followed by the application of the uPCR transition matrix. For example, if we consider a patient in CKD 1, with uPCR 1.0 – 3.0 g/g, receiving SOC treatment, and data from tables 66 and 73 from the original CS:
- i.** 90.17% of patients will remain in CKD 1 stage, out of which 74.66% of patients will remain in uPCR 1.0 – 3.0 g/g state, 12.95% will move to uPCR <1.0 g/g state and 12.40% will move to uPCR >3 g/g state

- ii. 9.83% of patients will move to CKD 2 stage, out of which 74.66% of patients will remain in uPCR 1.0 – 3.0 g/g state, 12.95% will move to uPCR <1.0 g/g state and 12.40% will move to uPCR >3 g/g state

Therefore, for a patient in CKD stage 1 with uPCR 1.0–3.0 g/g on SOC, the distribution between states after one cycle—without accounting for mortality—will be:

Table 51: Example CKD and UPCR distribution after one model cycle

	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
CKD 1	██████	██████	██████
CKD 2	██████	██████	██████

The transition matrices for SOC and pegcetacoplan are presented below (excluding transitions to dialysis and transplantation). Variability is considered separately in the model for uPCR and eGFR transitions. Transitions between uPCR states are included in the PSA using a Dirichlet distribution, while uncertainty in transitions between CKD stages is based on eGFR decline, modelled using a normal distribution.

Table 52: Transition matrix for SOC

	CKD 1; uPCR 1	CKD 1; uPCR 2	CKD 1; uPCR 3	CKD 2; uPCR 1	CKD 2; uPCR 2	CKD 2; uPCR 3	CKD 3; uPCR 1	CKD 3; uPCR 2	CKD 3; uPCR 3	CKD 4; uPCR 1	CKD 4; uPCR 2	CKD 4; uPCR 3	CKD 5; uPCR 1	CKD 5; uPCR 2	CKD 5; uPCR 3
CKD 1; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 1; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 1; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 2; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 2; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 2; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 3; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 3; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 3; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 4; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 4; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 4; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 5; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 5; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 5; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

Note: uPCR 1 – uPCR <1.0 g/g; uPCR 2 – uPCR 1.0 – 3.0 g/g; uPCR 3 – uPCR > 3.0 g/g

Table 53: Transition matrix for pegcetacoplan

	CKD 1; uPCR 1	CKD 1; uPCR 2	CKD 1; uPCR 3	CKD 2; uPCR 1	CKD 2; uPCR 2	CKD 2; uPCR 3	CKD 3; uPCR 1	CKD 3; uPCR 2	CKD 3; uPCR 3	CKD 4; uPCR 1	CKD 4; uPCR 2	CKD 4; uPCR 3	CKD 5; uPCR 1	CKD 5; uPCR 2	CKD 5; uPCR 3
CKD 1; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 1; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 1; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 2; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 2; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 2; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 3; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 3; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 3; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 4; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 4; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 4; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 5; uPCR 1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 5; uPCR 2	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
CKD 5; uPCR 3	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

Note: uPCR 1 – uPCR <1.0 g/g; uPCR 2 – uPCR 1.0 – 3.0 g/g; uPCR 3 – uPCR > 3.0 g/g

- b) Transition probabilities were estimated for 12 week cycles. Results reported for both multinomial regression for uPCR transition and linear regression for eGFR decline are for 12 week cycles, therefore there was no need for any data conversion to account for different cycle length.
- c) eGFR as a measurement often fluctuates over time, with transient increases and decreases commonly observed in clinical practice. Therefore, to more accurately assess the progression of chronic kidney disease, a sustained decrease in eGFR is typically required.

Table 54: Transitions rates by HS for pegcetacoplan

[illegible]

Cycle 2	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■
Cycle 3	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■
Cycle 4	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■

HS, health state; N, number

Table 55: Transitions rates by HS for SoC

Transition		HS 1 ↓ HS 1	HS 1 ↓ HS 2	HS 1 ↓ HS 3	HS 2 ↓ HS 1	HS 2 ↓ HS 2	HS 2 ↓ HS 3	HS 3 ↓ HS 1	HS 3 ↓ HS 2	HS 3 ↓ HS 3
Cycle 1	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■
Cycle 2	N subjects with transition	■	■	■	■	■	■	■	■	■
	N of subjects in cycle	■	■	■	■	■	■	■	■	■
	N dropouts in cycle	■	■	■	■	■	■	■	■	■
	Transition rate	■	■	■	■	■	■	■	■	■

HS, health state; N, number

B 13. Relative effectiveness versus iptacopan. CS section 3.3.2 describes the inclusion of iptacopan through applying an odds ratio (OR) of ■ (CS Table

68 provides results of Bucher's indirect comparison between pegcetacoplan and iptacopan for proteinuria-related outcomes [24h vs 24h]).

- a) Please provide full details for the calculated OR of [REDACTED], including the underlying trial data and any adjustments applied.
 - b) Please describe all assumptions underpinning the Bucher indirect comparison, including the choice of trials, population similarity, endpoint definitions, and any adjustments for baseline imbalances. Justify the appropriateness of these assumptions for estimating the relative effectiveness of pegcetacoplan versus iptacopan in the modelled population.
 - c) Please clarify how this OR can be derived from CS section 2.10 on indirect and mixed treatment comparisons.
 - d) Please justify that the OR of [REDACTED] (CS Table 68) are not used to inform the transition probabilities for iptacopan, also specifying the populations included.
 - e) Please provide the exact method, formula, and a worked example used to calculate the transition probabilities provided in CS Table 69. Include the full transition matrix with point estimates and 95% CIs for all transition probabilities.
 - f) Please justify why the OR for pegcetacoplan versus iptacopan was assumed to be constant over time (i.e. proportionality of the odds over time, and no waning of relative effectiveness) and provide evidence supporting this assumption.
 - g) Please justify that pegcetacoplan and iptacopan were only assumed to differ with regards to uPCR and confirm whether this assumption is consistent with the trial evidence and clinical plausibility.
- a) Thank you for your question. Table 56 below presents a summary of the patient level trial data

Table 56: Summary of trial outcomes informing the Bucher indirect comparison

Outcome	VALIANT (All patients)			APPEAR-C3G		
	PEG (N=63)	Placebo (N=61)	PEG vs Placebo	IPTA (N=38)	Placebo (N=36)	IPTA vs Placebo
24h(PEG) vs. 24h(IPTA)	uPCR (g/g), n (%) / OR [95% CI] , (n missing)					
≥3 uPCR				12 (32%) (1)	15 (42%)	0.65 [0.25; 1.67]
1 to <3 uPCR				21 (55%) (1)	19 (53%)	1.11 [0.44; 2.76]
<1 uPCR				4 (11%) (1)	2 (6%)	2.00 [0.34; 11.66]

The results of the Bucher's indirect comparison between pegcetacoplan and iptacopan based on the VALIANT and APPEAR-C3G trials are presented in .

Table 57: Bucher indirect comparison results

Outcome	VALIANT (All)	VALIANT (C3G)	Bucher's indirect comparison between VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	PEG vs Placebo	PEG vs IPTA
	OR [95% CI]		
uPCR 24h vs 24h			
≥3 (g/g)			
1-3 (g/g)			
<1 (g/g)			

- b) The indirect comparison was conducted using Bucher's method, based on data from two placebo-controlled RCTs with 6-month treatment durations: VALIANT (pegcetacoplan vs placebo) and APPEAR-C3G (iptacopan vs placebo). Both studies assessed proteinuria using uPCR (24-hour collection) at 6 months, providing a common endpoint for comparison. While the primary analysis in VALIANT used first-morning urine samples, 24-hour urine collections were also performed and reported, enabling consistent endpoint definitions across the two studies. As both included placebo arms and similar

outcome measures, these trials provide the most robust evidence base for an anchored indirect comparison of pegcetacoplan and iptacoplan.

Population similarity:

Overall, the study populations were broadly comparable with respect disease duration (<2 years) and baseline proteinuria; however, several notable differences were identified:

- Disease type: VALIANT included both C3G and IC-MPGN; APPEAR-C3G included only C3G.
- Serum C3 levels: Required $<0.85 \times \text{LLN}$ in APPEAR-C3G; not required in VALIANT ($\approx 40\%$ did not meet this criterion).
- Renal transplant: Allowed only in VALIANT (9 patients, 8 with C3G).
- Age: APPEAR-C3G enrolled adults, while VALIANT also included adolescents (<18 years)
- Renal biopsy: Mandatory in adults but optional for adolescents in VALIANT
- Sex: Fewer males in VALIANT (43% vs 64%)
- Disease subtype: IC-MPGN included only in VALIANT; among C3G, fewer DDD cases (8% vs 14%).
- Immunosuppressive use: Higher in VALIANT (73% vs 45%).
- Renal function: Lower mean eGFR in VALIANT (82 vs 94 mL/min/1.73m²); more patients with eGFR <90 (53% vs 42%) and <60 (33% vs 19%).

Despite these differences, subgroup analyses in VALIANT demonstrated consistent treatment effects across C3G and IC-MPGN, adults and adolescents, and transplant vs non-transplant patients. No statistically significant interactions were observed in proteinuria or eGFR outcomes, suggesting that these factors are unlikely to be major

effect modifiers. Therefore, the populations are considered sufficiently comparable to justify a Bucher ITC.

Appropriateness of assumptions:

The Bucher ITC was selected because:

- The method is well-established for anchored indirect comparisons and provides the most credible estimate of relative treatment effect when direct head-to-head evidence is unavailable. Bucher's method accounts for differences between studies through the common comparator (placebo), thereby indirectly controlling for study-level confounding.
- Both trials were randomized, placebo-controlled, and reported the same endpoint at the same time point.
- The absence of significant effect modification across key subgroups in VALIANT supports the assumption of transitivity.
- As noted by the External Assessment Group (York), Bucher's ITC remains appropriate even when potential imbalances in effect modifiers cannot be fully excluded, provided the evidence base is anchored through a common comparator (see NICE TA1000 committee papers: [link](#)).

In summary, the Bucher indirect comparison rests on the assumptions of population similarity, consistent endpoint definitions, and no major effect modification. Based on the available evidence, these assumptions are reasonable and appropriate for estimating the relative effectiveness of pegcetacoplan versus iptacopan in the modelled population.

- c) The OR of 2.46 corresponds to the comparison between PEG and IPTA using the same methods of proteinuria estimation (24h in both trials), while the ORs in section 2.10 correspond to the comparison of primary methods of estimation in the respective studies (first morning urine in VALIANT and 24h in APPEAR-C3G).

d) Due to limited data availability for iptacopan, there is no single correct method for calculating transition probabilities for this drug based on the results of the Bucher indirect treatment comparison. The use of OR of 0.60 for the transition to uPCR > 3 g/g may be problematic, as no such transitions were observed for pegcetacoplan from uPCR < 1.0 g/g to > 3 g/g. Consequently, the relative effect between drugs for this specific transition cannot be maintained in the model. Therefore, it was conservatively assumed that no such transitions occur for iptacopan either.

Excluding the use of OR for uPCR > 3 g/g, there are two possible approaches:

1. Use of the OR for uPCR < 1 g/g to estimate the probability of transitioning to the uPCR < 1.0 g/g state, with proportional adjustment of the remaining transitions.
2. Use of ORs for both uPCR < 1 g/g and 1–3 g/g, applying them to the corresponding transitions, and calculating the remaining transition (to > 3 g/g) as the complement to 100%.

The first approach was applied in the model, as the transition to uPCR < 1 g/g represents the most clinically significant outcome. However, the second approach is also expected to yield consistent results.

The table below presents the iptacopan transition probabilities derived using the second approach. Due to the higher estimated probabilities of transitioning to uPCR > 3 g/g, this matrix is considered less conservative than the one used in the CS.

uPCR transitions with iptacopan

From\To	uPCR <1.0 g/g	uPCR 1.0 - 3.0 g/g	uPCR >3 g/g
uPCR <1.0 g/g	██████	██████	██████
uPCR 1.0 - 3.0 g/g	██████	██████	██████
uPCR >3 g/g	██████	██████	██████

Abbreviations: UPCR, urine protein-creatinine ratio

Table 58: Scenario analysis - alternative method for calculating iptacopan UPCR transitions using OR derived from Bucher indirect comparison

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
'New' base case					£35,798	Dominant
Alternative method of calculating iptacopan UPCR transitions using OR from Bucher indirect comparison					£35,798	Dominant

e) The transition probabilities presented in CS Table 69 were calculated as follows:

1. Transitions to the uPCR < 1.0 g/g state were derived directly from the corresponding pegcetacoplan transitions (e.g., 87.26%) and the odds ratio (OR) for uPCR < 1.0 g/g (2.46), using the following steps:
 - i. First, odds for pegcetacoplan were calculated, e.g., $87.26\% / (1 - 87.26\%) = 6.85$
 - ii. The OR was applied to obtain the odds for iptacopan: $6.85 / 2.46 = 2.79$
 - iii. These odds were then converted back to probability: $2.79 / (1 + 2.79) = 73.58\%$
2. The remaining transitions were calculated proportionally to the pegcetacoplan probabilities. For example:
 - i. $(1 - 73.58\%) \times (12.74\% / (12.74\% + 0.00\%)) = 26.42\%$

- ii. In this example, the probability of transitioning to uPCR > 3 g/g for pegcetacoplan was zero, but it was retained in the formula to demonstrate the calculation principle.

Uncertainty around the iptacopan transition probabilities was derived from two sources:

- i. The known uncertainty in the OR (95% CI)
- ii. The uncertainty in the pegcetacoplan transitions, using bootstrapped standard errors (SEs)

The OR was incorporated explicitly in the updated model as an input, used to derive iptacopan transitions from pegcetacoplan transitions.

For the PSA, probabilistic draws for the OR were generated by sampling from a normal distribution on the log(OR) scale, and then exponentiating the samples to obtain ORs. These were subsequently applied to the probabilistic pegcetacoplan transitions to derive corresponding iptacopan transitions.

- f) As outlined in the response to B16, no treatment waning is anticipated for patients receiving pegcetacoplan, based on expert clinical input and the known mechanism of action of pegcetacoplan. Furthermore, this assumption is consistent with the committee's conclusion during ACM1 for iptacopan in C3G (GID-TA11331), wherein iptacopan's mechanism of action was considered to justify a constant treatment effect as a reasonable assumption.
- g) Since uPCR is the primary driver of outcomes in the model, it was considered essential to differentiate between pegcetacoplan and iptacopan with respect to this clinical endpoint. This differentiation has a direct impact on the estimated differences in costs and QALYs between the two treatments, thereby enabling robust conclusions to be drawn regarding their relative cost-effectiveness.

Given the limited availability of clinical data for iptacopan, incorporating this differentiation was considered the most appropriate approach to ensure accurate modelling of cost-effectiveness—while also avoiding any risk of

double counting the benefits associated with pegcetacoplan relative to iptacopan.

B 14. The CS appears to apply identical transition probabilities pre- and post-transplant. Clarification is requested on the assumption of identical transition probabilities before and after transplant, to assess clinical plausibility and consistency with trial data.

- a) Please provide clinical justification and supporting evidence for treating transition probabilities pre- and post-transplant as equal (or, if not equal, specify differences).
 - b) If any parameters were assumed identical due to data limitations (e.g. lack of post-transplant trial data), please provide scenario analyses (and an updated model) applying clinically plausible alternative post-transplant transition profiles (including at least one scenario with faster deterioration post-subsequent transplants). Present effects on modelled time to dialysis, QALYs, and costs.
- a) Due to the limited availability of post-transplant data in both VALIANT and external sources—particularly regarding changes in UPCR—the assumption of constant transition probabilities before and after transplant was a necessary simplification. Anecdotal clinical feedback received prior to submission suggested that transplanted kidneys tend to deteriorate more rapidly than native kidneys, as patients have only half the normal nephron mass and are exposed to nephrotoxic immunosuppressive medications that can further accelerate decline.
 - b) Unfortunately, given the current model structure and the additional time required to incorporate differential transition rates, it was not feasible to reflect this dynamic within the model. It is hypothesised, however, that if post-transplant UPCR deterioration were faster than that observed in native kidneys, the results would likely favour pegcetacoplan. This is because transplanted patients—who are more prevalent in the SOC arm—would be expected to progress more quickly to the more costly and lower-utility health states (CKD 4, CKD 5, dialysis, and subsequent transplants), thereby

worsening outcomes and costs in the SOC arm relative to pegcetacoplan. As such, the base-case assumption can be considered conservative with respect to post-transplant disease progression.

Assumptions related to disease progression

- B 15. Priority question. Stable disease assumptions. Clarification is requested on the definition, implementation, and impact of the ‘stable disease’ health state, to determine whether it is necessary and appropriately incorporated in the model.**
- a) Please justify the necessity to include a “stable disease” label to a specific subpopulation, especially given the CS base-case already is categorising patients into uPCR categories, modelling “stable disease” appears to be redundant.**
 - b) Please justify the appropriateness of the inclusion of ‘stable disease’. In particular, explain to what degree the calculated transition probabilities already incorporate potential reductions in progression risks (associated to the health state) and how double-counting is avoided.**
 - c) Please provide evidence from the VALIANT study supporting the existence of a “stable disease” phase (where patients “maintained stable eGFR”) and provide relevant information for these patients including treatment arm, eGFR, uPCR as well as whether these patients discontinued treatment.**
 - d) Please justify the relevance of Caravaca-Fontán 2020 () (which is based on corticosteroids plus MMF) for estimating stable disease probabilities after pegcetacoplan treatment.**
 - e) Patients in the stable disease state are not assumed to experience eGFR decline or transition to later CKD stages. Please justify this assumption.**

f) Please provide evidence on the relationship between stable uPCR and long-term eGFR decline from

i. VALIANT

ii. external studies.

g) Please clarify how “stable disease” is exactly implemented in the economic model and provide justification if it is not implemented as a health state.

h) Please clarify whether patients that are classified as “stable disease” can transition back to non-stable disease (i.e., loss of stable disease) and then re-enter stable disease subsequently. If so, how many such transitions are possible? Please support your response with VALIANT data.

i) Please reproduce CS Table 76, restricting the trial data up to 26 weeks for both treatment strategies, to ensure consistency of observation windows.

j) To explore the impact of using different assumptions related to “stable disease”, please provide scenario analyses as well as an updated economic model:

i. applying the exact definition of “stable disease” from Caravaca-Fontán 2020() (uPCR <1/0 g/g).

ii. applying a more stringent definition of “stable disease” (uPCR <0.3 g/g).

iii. restricting the trial data up to 26 weeks to estimate the probability of disease stabilisation (CS Table 76) for both treatment strategies

iv. using shorter median durations of stable disease than in CS Table 77, including 3, 6, 12, 18, and 24 months.

v. assuming eGFR decline for patients in “stable disease”.

vi. assume no treatment discontinuation for “stable disease”

vii. assuming no stable disease occurs for either treatment strategy.

- a) Stable disease or remission is a recognised treatment goal in glomerulonephritides such as C3G and IC-MPGN. For therapies with potential disease-modifying effects, including complement inhibitors such as pegcetacoplan, clinicians may consider structured treatment withdrawal in responders, with close monitoring to assess durability of remission and the option to re-introduce if relapse occurs.

An analogue exists in atypical haemolytic uraemic syndrome (aHUS), where a prospective single-arm study of protocolised eculizumab discontinuation in selected patients showed no signal of excess harm (Bryant et al, 2025).

Accordingly, in clinical practice clinicians are increasingly considering monitored withdrawal for select patients.

The Company therefore included a stable disease state in the model in which patients may discontinue treatment. In particular, the modelling of a separate “stable disease” health state was incorporated following initial feedback from clinicians who indicated that patients who show signs of achieving good disease control whilst on treatment, based on a sustained low UPCR level, may attempt to take patients off active treatment, with the caveat that if proteinuria returned then they would restart treatment. As such, some patients in the UPCR <1.0g/g sub-group may be considered to have “stable disease” and taken off treatment, therefore, no acquisition costs are incurred for these patients in the model. However, patients with UPCR <1.0g/g but not considered to have stable disease are assumed to remain on active treatment and incur the respective costs in the model.

In the model base case the probability of a patient with UPCR <1.0 g/g transitioning to the “stable disease” health state was calculated using the likelihood of patients with UPCR <1.0 g/g in VALIANT reaching a lower

threshold UPCR value of $<0.5\text{g/g}$ in a 3-month (1-cycle) period, corresponding to:

- i. Pegcetacoplan: 31.07%
- ii. Standard of care: 13.40%
- iii. Iptacopan: 15.48%

Please see section 3.3.3 of the CS for more details on how these figures were derived.

- b) The Company consider there to be no risk of double counting, as no additional clinical effect is applied to patients with stable disease in the pegcetacoplan arm. Based on the statistical analysis of the trial data, patients treated with pegcetacoplan who achieved $\text{uPCR} < 1.0\text{ g/g}$ showed an increase in eGFR, indicating stabilisation of kidney function. However, extrapolating this short-term improvement in eGFR over the full model time horizon was deemed inappropriate. Therefore, a conservative assumption was adopted: no change in eGFR was applied for patients with $\text{uPCR} < 1.0\text{ g/g}$ while receiving pegcetacoplan.

This conservative approach was further extended to all patients who transitioned to stable disease, regardless of treatment arm. Notably, the model also allows patients receiving SoC to achieve remission. For these patients, no eGFR decline is assumed, even though trial data showed a mean decline among all patients with $\text{uPCR} < 1.0\text{ g/g}$ while on SoC. From this perspective, the inclusion of a stable disease state in the model actually reduces the relative benefit of pegcetacoplan over SoC.

- c) According to the study protocol of VALIANT, treatment discontinuation due to disease stabilisation was not permitted. Allowing such discontinuation would have undermined the trial's statistical integrity and the interpretability of its endpoints.

Regarding patients on SoC who had stable disease at 26 weeks, these individuals achieved $\text{uPCR} < 0.5\text{ g/g}$ towards the end of the trial. Therefore, their eGFR data should not be interpreted as reflective of sustained disease

stabilisation. Nonetheless, the average eGFR change for patients who reached uPCR < 0.5 g/g on SoC was –2.17 per 12 weeks.

In contrast, patients treated with pegcetacoplan achieved uPCR < 0.5 g/g earlier in the study, meaning that the calculated average eGFR change per 12 weeks is more indicative of the presence and effect of stable disease.

Depending on the follow-up period analysed, the average eGFR change was estimated at +2.04 (over 52 weeks) and +2.47 (over 26 weeks), suggesting disease stabilisation accompanied by improved kidney function.

It is also worth noting that, on average, all patients receiving pegcetacoplan with uPCR < 1.0 g/g experienced an increase in eGFR. However, this improvement was conservatively not included in the model; instead, a neutral assumption of no eGFR worsening was applied.

- d) Caravaca-Fontán 2020 was referenced to support the concept and definition of stable disease, and to illustrate its recognition and assessment in clinical practice. However, this source was not used to estimate the probability of achieving stable disease following pegcetacoplan treatment. Those probabilities were derived directly from the VALIANT trial data, based on the definitions applied within the model.

That said, Caravaca-Fontán 2020 was used to inform the probability of disease relapse among patients in the stable disease state. Specifically, the relapse probability was estimated based on the observed median duration of stable disease in patients treated with corticosteroids plus MMF, as reported in the study.

In response to this question, additional UK clinical expert opinion was sought to determine the relevance of defining stable disease in patients with C3G/IC-MPGN in a similar manner to that used in the Caravaca-Fontán 2020.

Feedback received indicated that the use of proteinuria threshold was appropriate, although there were differences with regards to the threshold experts would consider stopping treatment at: some were comfortable with <0.5 g/24 h; others preferred <0.3 g/24 h. One clinician did highlight that a preferred way to decide if stopping treatment was suitable would be to

measure nephritic factors (for those in whom nephritic factors had previously been identified) as absence of nephritic factors would indicate the driver for complement dysregulation would have gone away. However, it was acknowledged that further research and better access to such investigation in clinical practice would be required and so, for purposes of modelling, they considered a UPCR threshold of 0.5g/24h although preferred a 0.3g/24h cut off.

In the majority of expert clinical feedback, the use of an eGFR threshold was not considered appropriate as even patients with low eGFR (≤ 60 ml/min per 1.73 m^2), who had shown stabilisation in their eGFR, may still be considered to have “stable disease”, if combined with low UPCR levels.

- e) This assumption directly follows from the definition of stable disease, which refers to the stabilisation of eGFR. It is important to note that, based on the regression analysis performed to estimate eGFR decline by uPCR level, all patients with uPCR < 1.0 g/g treated with pegcetacoplan showed an increase in eGFR, indicating a stabilisation—or even improvement—of kidney function. However, extrapolating this observed improvement over the full model time horizon was considered inappropriate.

Therefore, a conservative assumption was applied: no change in eGFR was assumed for patients with uPCR < 1.0 g/g while on pegcetacoplan treatment. This assumption was subsequently extended to all patients transitioning to the stable disease state, regardless of treatment arm.

Notably, the model also allows patients on SoC to achieve remission. For these patients, no eGFR decline is applied either, even though the trial data showed a mean decline among all patients with uPCR < 1.0 g/g receiving SoC. From this perspective, the assumption of no eGFR decline in a stable disease state in the model is conservative and, in fact, reduces the relative benefit of pegcetacoplan compared to SoC.

Clinical input was also sought in response to this query, with a mix of feedback received with regards to whether they may expect to see eGFR decline in those patients considered to have “stable disease”. However, the

majority did consider that stabilisation of eGFR is an important factor when considering if a patient has “stable disease” or not.

Although VALIANT trial data suggest that patients with UPCR < 1.0 g/g experienced improvements in eGFR, the potential long-term implications of incorporating this assumption into the model led to the adoption of a conservative approach—assuming no change in eGFR for this subgroup. This assumption may, in fact, favour SOC, as it allows SOC patients in the “stable disease” health state to gain both cost and health benefits from treatment stopping and eGFR stabilisation, since SOC patients with UPCR < 1.0 g/g who are not in stable disease would otherwise experience an eGFR decline of –1.471. In contrast, pegcetacoplan patients derive only cost benefits under this assumption as pegcetacoplan patients with UPCR <1.0g/g are already assumed to have eGFR stabilisation based on VALIANT data.

- f) The relationship between stable UPCR and long-term eGFR decline is comprehensively addressed in the “Relationship between eGFR and UPCR” section (Section 3.3.1) of the CS. This section summarises several external studies demonstrating that higher UPCR levels are associated with faster declines in eGFR, while lower proteinuria levels are linked to a reduced risk of significant eGFR decline. Of particular relevance to this question, findings from Caravaca-Fontán (2025) emphasise the importance of not only achieving short-term reductions in proteinuria but also maintaining an optimal target of <1 g/day over time to effectively slow disease progression in C3G and IC-MPGN.

Data from VALIANT have also been used to identify a relationship between UPCR and eGFR which was subsequently used in the model to inform average change in eGFR by UPCR sub-groups. However, due to available VALIANT data being limited to 52-weeks, it is not considered possible to use this data to elicit long term relationships between these two measures, as such, the literature in Section 3.3.1 of the CS were used to help validate the sustained long-term relationship used in the model.

- g) Stable disease is appropriately considered a health state in the model, as it possesses all the characteristics expected of a modelled health state—for example, specific cost and utility values are assigned to patients in this state. Technically, it is implemented in the same way as the other health states in the model. The key difference lies in the source of data used to inform the transition probabilities into this state.

Specifically, the probability of achieving remission (i.e., transitioning to the stable disease state) was derived from the VALIANT trial, based on the number of patients who met the criteria for stable disease at the end of follow-up—26 weeks for the placebo group and 52 weeks for the pegcetacoplan group.

However, due to the limited duration of the trial, data on the long-term sustainability of stable disease were not available. Although all patients who achieved stable disease while on pegcetacoplan showed, on average, improvements in eGFR, it was considered inappropriate to assume that this stable disease state would persist indefinitely. This is especially important in light of evidence from Caravaca-Fontán et al. 2020, which suggests that relapse can occur after treatment discontinuation. Moreover, treatment discontinuation after achieving stable disease was not allowed in VALIANT.

Assuming no relapse would risk overestimating the clinical benefit of pegcetacoplan. Therefore, relapse probabilities were estimated based on the median duration of stable disease reported in Caravaca-Fontán 2020 for patients treated with corticosteroids plus MMF, and applied accordingly in the model.

- h) In VALIANT, all patients who achieved stable disease while on pegcetacoplan showed, on average, improvements in eGFR. However, treatment discontinuation after achieving stable disease was not permitted in the VALIANT trial. Therefore, it was considered inappropriate to assume indefinite duration in the stable disease state. To avoid overestimating the treatment benefit, a probability of disease relapse was incorporated into the model, informed by available literature.

Importantly, disease stabilisation was initially observed in patients with high baseline UPCR levels, following treatment with pegcetacoplan. Relapse, characterised by an increase in UPCR, is associated with treatment interruption. Given that treatment was able to induce stabilisation even in patients with high baseline UPCR levels, it is reasonable to assume that reinitiated treatment following relapse would be similarly effective—particularly as patients' UPCR levels at the time of treatment reinitiation would likely be lower than at VALIANT baseline.

Consistent with the structure applied to all other health states (except death), the model allows for unrestricted transitions to and from the stable disease state.

i) Updated CS Table 76 for pegcetacoplan is presented below

Table 59: Probability of disease stabilisation

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	■	■	■

j) Please see a summary of the requested scenarios in Table 60.

Table 60: Scenarios relating to "stable disease" assumptions in the model

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Base case	■	■	■	■	£35,798	Dominant
UPCR <1.0 g/g	■	■	■	■	£88,131	Dominant
UPCR <0.3 g/g	■	■	■	■	£34,069	Dominant
Restricting to 26-week trial data only	■	■	■	■	£25,391	Dominant

Shorter median duration of stable disease – 24 months		£39,676	Dominant
Shorter median duration of stable disease – 18 months		£54,883	Dominant
Shorter median duration of stable disease – 12 months		£79,100	Dominant
eGFR decline in “stable disease”		£39,375	Dominant
No treatment discontinuation in “stable disease”		£335,344	Dominant
No stable disease		£272,573	Dominant

B 16. Priority question. Treatment effect waning. Evidence and scenario analyses are requested regarding the assumption of a constant pegcetacoplan treatment effect, to evaluate the impact of potential treatment waning on model outcomes.

- a) Please justify the assumption of no treatment waning, i.e. that there is a constant lifetime pegcetacoplan treatment effect.
- b) Please provide evidence (trial data or external) that justifies the assumption of no waning.
- c) Please provide scenario analyses and an updated economic model exploring treatment effect waning, including at least the following:
 - i. No waning (base-case);
 - ii. Gradual waning beginning at 2, 5, and 10 years (assume linear decline to zero effect over 5 years);

- iii. Instant (complete) waning at 2, 5 and 10 years.
- d) Please provide time-to-event data on CKD progression (i.e., CKD progression-free survival) for pegcetacoplan + SoC versus SoC alone. Specifically, please analyse time-to-event data separately for progression to CKD stages 2, 3, 4, and 5, as well as for time to dialysis, death, or transplant:**
- i. Handling of patients with prior events: if patients already had the event before the analysis started (e.g., patients in CKD stage 2 for the time-to-CKD-stage-2 analysis), please include these patients as having the event at day 1.
 - ii. Tabulated data: provide time-to-event data at different time points for CKD stages 2, 3, 4, and 5 for both treatment arms.
 - iii. Kaplan-Meier plots: present Kaplan-Meier survival curves for CKD progression-free survival, stratified by treatment arm. Include the number of patients at risk at multiple time points (e.g. every month).
 - iv. Hazard plots: provide hazard plots over time.
 - v. Cumulative hazard plots: provide cumulative hazard plots over time.
 - vi. Cox proportional hazards analysis: perform a Cox regression analysis and include Schoenfeld residuals plots to assess the proportional hazards assumption.
- e) Please justify, based on the analyses above, assuming a constant treatment effect of pegcetacoplan over the model time horizon.**
- a) As outlined in Table 62 of the CS, this modelling assumption was informed by clinical expert opinion obtained prior to submission. Experts noted that the mode of action of pegcetacoplan—blocking overactivation of the alternative pathway and reducing C3 deposition in the glomeruli—is well established and directly aligned with the known disease mechanisms of C3G and IC-MPGN.

Both conditions are driven by dysregulation of the alternative pathway, leading to excessive C3 activation, formation of C3b, and deposition of C3 fragments in the glomeruli, causing inflammation and kidney damage. By inhibiting C3, pegcetacoplan acts upstream in the complement cascade to prevent this overactivation and subsequent tissue injury. Based on this well-understood mode of action, experts concluded there is no scientific rationale to expect the pharmacological effect of pegcetacoplan to wane over time.

Figure 10 and Figure 11 provide new data from VALE showing no waning effect (up to week 100) – this is an updated analysis that provides an update for Figure 12 and 13 from the CS. Figure 12 and 13 from the CS were based from an old data cut from June 2024 where a lower proportion of patients had long enough follow up – the new data are from September 2025 and were not available at the time of the submission.

Figure 10: Mean ($\pm$ SE) Change from Re-Aligned Baseline of eGFR (mL/min/1.73 m²) - Combined Analysis - Re-Aligned ITT Set, reduced number of visit windows for both arms - Studies 310 + 314 (10SEP2025)

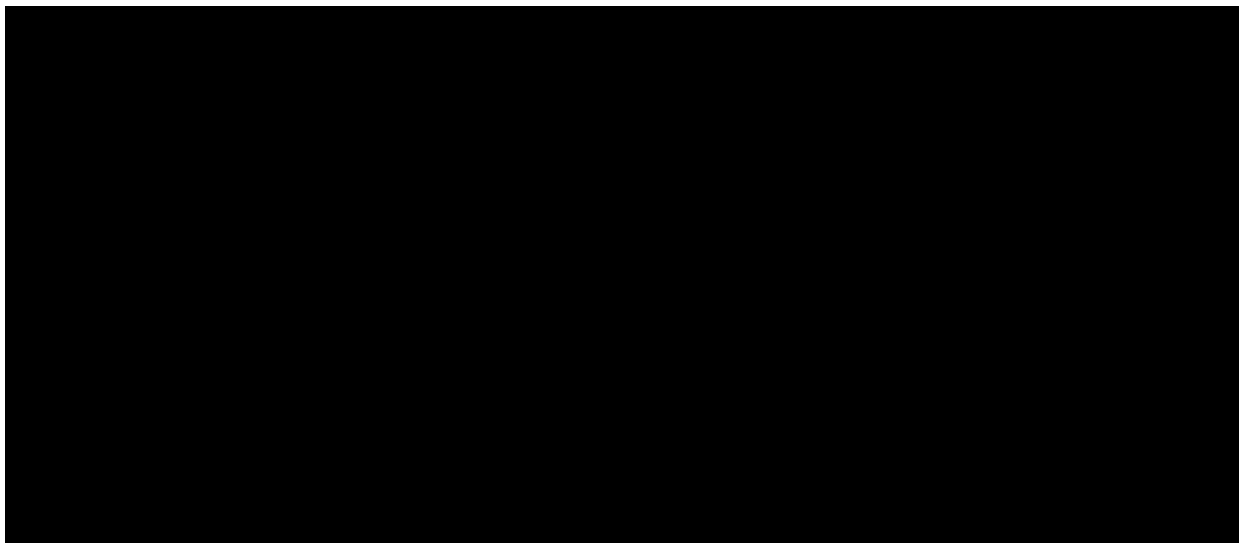
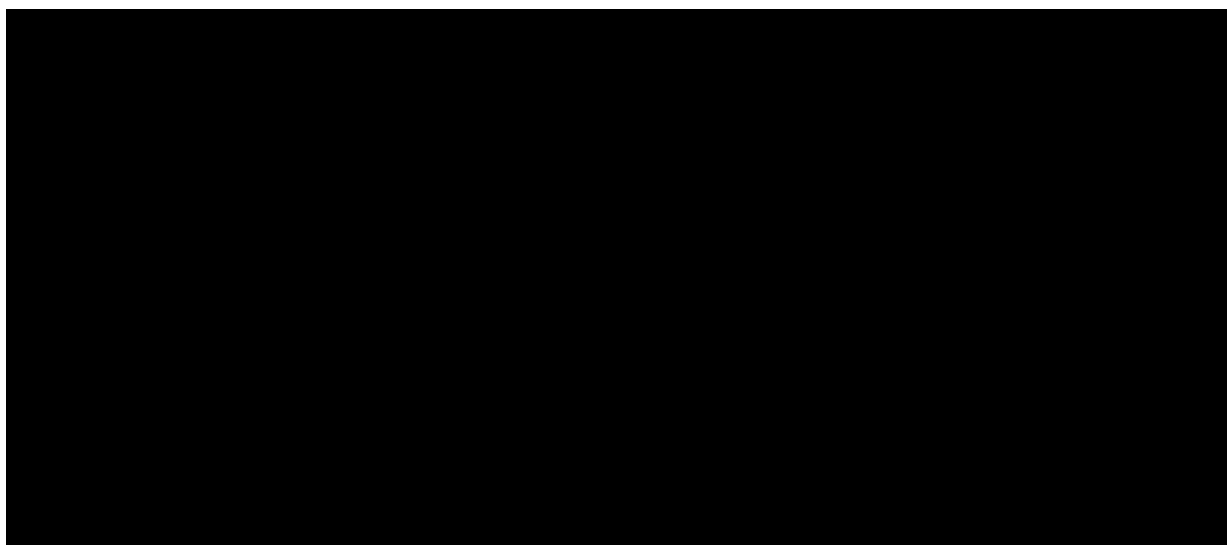


Figure 11: Geometric Mean (95% CI) Ratio to Baseline of FMU uPCR - Combined Analysis - Re-Aligned ITT Set, reduced number of visit windows for both arms - Studies 310 + 314 (10SEP2025)



Additionally, Table 62 of the CS notes that the assumption of no treatment waning is consistent with the committee's preferred assumption following the first committee meeting for the ongoing iptacopan appraisal. Given that both pegcetacoplan and iptacopan act on the complement system and aim to reduce C3 deposition in the glomeruli, it is considered appropriate to apply a similar assumption of no treatment waning for pegcetacoplan.

- b) Following on from the response to B16a, long-term outcomes from other indications in which pegcetacoplan is indicated (PNH) demonstrate a sustained C3 inhibition. In particular, de Castro et al. 2025 demonstrated sustained efficacy of pegcetacoplan at least up to 3 years using integrated analysis of clinical trial data including PEGASUS, PRINCE and subsequent open-label extensions.
- c) Based on the data provided and the expert clinical feedback outlined in responses to B16a and B16b, it is not considered appropriate to conduct the requested scenarios. Expert opinion, longer-term clinical evidence, and precedent from similar NICE appraisals all indicate that these scenarios are unlikely to occur in clinical practice.
- d) Detailed time-to-event analyses for CKD progression was requested. While we acknowledge this request, we have significant concerns regarding its feasibility and clinical appropriateness due to the following key points:

- i. **Limited Data & Statistical Power:** The trials were not designed for these endpoints. The number of patients progressing to advanced CKD stages (4, 5), dialysis, or transplant during the trial is very low. Some patients showed transient worsening of CKD stage at a single visit, which does not indicate true progression. Including these as events would overestimate progression. Any stage-specific survival analyses would be statistically underpowered and highly exploratory.
 - ii. **Methodological Concerns with Baseline Events:** The proposed method of counting patients with a baseline event (e.g., already at CKD stage 3) as having an event at "Day 1" conflates baseline severity with treatment effect and is inconsistent with the incremental nature of CKD progression and standard survival analysis methodology.
 - iii. **Unreliable Outputs:** Given the sparse data, requested analyses (Kaplan-Meier plots, Cox models) would be unstable and potentially misleading. Key model assumptions, like proportional hazards, are unlikely to be met.
- e) The Company believe the justification for assuming a constant treatment effect has been addressed in responses B16a-b.

Assumptions related to additional benefits

- B 17. Cardiovascular (CV) events. Justification and supporting evidence are requested for inclusion of CV events in the model, to assess whether they are relevant and accurately modelled for the target population.
- a) Please clarify how the sources reported in CS Table 78 were identified.
 - b) Please justify the appropriateness of the sources reported in CS Table 78 to estimate CV events for the current decision problem.
 - c) Provide the mathematical steps and worked example used to calculate the probabilities of health events per cycle (CS Table 79) and the impact of CKD on the risk of health events (CS Table 80). Explicitly state any assumptions.

d) Please justify the inclusion of CV events in the model. Specifically:

- i. Provide evidence that the assumed relationship between CKD/uPCR and CV events is applicable to the population considered in the current assessment.
- ii. Justify the choice of cut-off (~ 90 mL/min/1.73 m²) and clarify whether this reflects UK clinical practice.
- iii. Explain the assumed duration of treatment effect on CV risk and whether prior/current treatments (including pegcetacoplan) are assumed to modify CV risk.

e) Please report whether any CV events occurred in APPEAR-C3G and VALIANT (tabulate number and type by arm and timepoint) and explain how trial CV data were incorporated into the model.

f) Please justify the consistency of the current approach with previous NICE TAs and published CEAs. If deviations exist, please provide a rationale.

g) Please provide scenario analyses and an updated economic model excluding CV events and report the impact on cost-effectiveness results.

a,b,d-g) Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to address this point in full at this time. If the issue becomes a priority, it will be considered further, and additional details can be provided if requested.

However, given the life-extending nature of pegcetacoplan, it is expected that removing cardiovascular (CV) events from the model would favour the SOC arm, as demonstrated in the analysis conducted in response to B4e. This is because patients receiving pegcetacoplan remain alive for longer within the model and therefore accumulate a higher lifetime risk of CV events, despite spending more time in less severe health states where the per-cycle risk of such events is anticipated to be lower.

c) The Company thanks the EAG for this clarification request.

Events are adjusted to per-cycle probability using equation:

$$1 - (1 - \text{annual probability})^{\frac{1}{4}}$$

While hazard ratios are applied using:

$$1 - (1 - \text{base probability})^{HR}$$

Annual incidence of stroke is 0.9%

It is recalculated to stroke probability per 3-months using equation:

$$1 - (1 - 0.9\%)^{\frac{1}{4}} \text{ which equals to around } 0.23\%.$$

For CKD stage 5 HR for stroke equals 1.52, therefore probability of stroke for CKD 5 is calculated as: $1 - (1 - 0.23\%)^{1.52}$

- B 18. Impact of CKD on mortality. Clarification and justification are requested for the hazard ratios applied for CKD-related mortality, to ensure consistency with trial/external data and prior NICE appraisals.
- a) Please provide justification and sources for the hazard ratios (HRs) applied to capture the impact of CKD stage on all-cause mortality in the model (tabulate HRs and cite original sources).
 - b) The HRs applied appear to be higher than those reported in prior NICE TAs and external literature. For instance in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy) the HR was 1.32 for CKD stages 1-4 and 3.99 for CKD stage 5 as well as on dialysis and post transplant (CS Table 39 in: <https://www.nice.org.uk/guidance/gid-ta11331/documents/committee-papers>). Please cross-check against published NICE TAs and reconcile any differences.
 - c) Please provide scenario analyses applying alternative HRs from GID-TA11331.
 - a) Please see Table 81 of the CS which outlines the hazard ratios from Quist 2025 applied in the model. The original source for these data was taken from Darlington et al. 2021 which was identified as the most robust source in

previous NICE appraisals (TA877). The hazard ratios presented in Darlington 2021 were derived from 323 studies that met the inclusion criteria and reported associations between CKD stage and all-cause mortality.

We appreciate the EAG bringing this to our attention. As these data were reportedly for patients with baseline diabetes comorbidities, which more closely reflected the patient population considered in TA877. As pegcetacoplan is not considered to be limited to patients with diabetes, the “Entire cohort” values from Darlington et al. 2021 are considered more appropriate for this appraisal.

Table 61: Summary of HRs considered in the model

CKD stage	GID-TA11331	Original CS base case (Quist et al 2025/Darlington et al. 2021)	Darlington et al. 2021 – Entire cohort	Notes
CKD 1	1.32	1.14	1.00	Assumed equivalent to CKD 2 values
CKD 2	1.32	1.14	1.11	
CKD 3	1.32	1.33	1.88	Calculated as the average of HRs for CKD 3a and 3b
CKD 4	1.32	6.42	3.01	
CKD 5	3.99	9.49	4.26	

Following the amendment to the HRs used in the Companies updated base case, to reflect the “Entire cohort” values from Darlington et al. 2021, these HRs are more aligned with values used in the iptacopan appraisal, with the potential exception of CKD 4 estimates which are higher than those reported in GID-TA11331.

The general trend in increased risk of mortality as patients progress through the CKD stages is aligned with expert clinical feedback sought following clarification questions where clinicians felt it was plausible that the risk of death would continue to increase as patients progressed through CKD stages.

Table 62: Summary of change to original model base case (from CS) following changes to CKD HR

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Original CS - Base case					£28,714	Dominant
Updated all-cause mortality HR from Entire cohort in Darlington et al. 2021					£27,168	Dominant

- b) As outlined in response to B18a, following an update to the source data used in the base economic analysis, the HR values used are now more aligned with values used in the iptacopan appraisal for C3G.
- c) Outcomes from the scenario in which HR values from the iptacopan appraisal were used is outlined in Table 63.

Table 63: Scenario using CKD related HR from GID-TA11331

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Base case					£35,798	Dominant
CKD mortality HRs from GID-TA11331					£29,706	Dominant

Adverse events

B 19. Priority question. In CS 3.3.7, the company stated that no adverse events were considered in the economic modelling as few patients in each VALIANT treatment arm experienced serious treatment-emergent adverse events during its randomized controlled period. However, in CS

sections 3.4.5 and 3.5.5., disutilities and costs were assigned to adverse reactions due to cardiovascular events.

- a) Please explain this inconsistency, and why particularly cardiovascular events should be incorporated despite the findings and thresholds applied on the clinical trial data (see clarification question B17).
- b) Please justify the different sources that inform cardiovascular events in the model. How do these compare to VALIANT and are these reflective of UK clinical practice?
- c) Please explain the rationale and thresholds (i.e., adverse events classification criteria) of including serious adverse events which were considered “treatment-emergent”.
- d) In the APL2-C3G-310 Final Clinical Study Report, section 9.7.2.1., it was stated that “If a PT [Preferred Term] was reported more than once for the same participant, that participant would only be counted once in the incidence for that PT.” Please discuss the rationale and potential shortcomings of this approach.
- e) Please perform a SLR on published evidence as well as TAs to cross-validate adverse events sourced from VALIANT.
- f) Please provide an updated economic model and scenario analyses for the VALIANT randomised controlled period including the following alternatives each, allowing for a patient being counted each time they experienced a PT.
 - i. All SAEs irrespective of suspected relationship with pegcetacoplan and grade.
 - ii. All grade ≥ 3 AE (i.e. incidence $>0\%$).
 - iii. All grade ≥ 3 AE with an incidence of $\geq 5\%$.

g) Please perform a SLR on published evidence and prior TAs to address adverse events apparent in later stages in the CS patient population, which were potentially not captured in VALIANT.

h) Please provide an updated economic model and scenario analyses for the adverse events sourced in f), for the following alternatives each.

i. All grade ≥ 3 AE (i.e. incidence $>0\%$).

ii. All grade ≥ 3 AE with an incidence of $\geq 5\%$.

a) Although evidence specific to C3G and primary IC-MPGN as ultra-rare diseases is limited, it is well established that worsening kidney function is linked to a higher risk of kidney-related complications, including cardiovascular disease and increased mortality (16) (1) (18) (19) (20). Accordingly, CV events were incorporated into the model to reflect the relationship between worsening kidney function, as represented by progression through CKD health states, and an elevated risk of CV events.

CV events are treated as distinct from adverse events, which are typically related to treatment use. While no CV events were observed in the VALIANT study, their exclusion from the model is not considered appropriate, as VALIANT was not designed or powered to assess the association between kidney damage and CV risk. Nonetheless, evidence from the broader literature supports the existence of this relationship, and it is therefore considered appropriate to account for it within the model.

b) Thank you for bringing this to the Company's attention. Upon further review of the literature, the original values used in the company base case may have been overestimated and that CV events are likely less common in younger C3G patients, as suggested by the EAG. For this reason, a scenario excluding these events was run which results in marginally improved outcomes, as outlined in Table 14.

c) To clarify, a treatment-emergent adverse event (TEAE) was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last

dose of study drug. A threshold of $\geq 5\%$ was implemented as an example of a common threshold used to avoid inclusion of adverse events within the model which could be considered random and part of the general health of the trial population rather than necessary treatment safety related.

- d) Counting each participant only once per Preferred Term (PT) ensures that incidence reflects the proportion of participants affected, not the number of events. This approach provides a participant-based measure rather than an event-based one, which is appropriate when the goal is to understand how many individuals experienced a specific adverse event (AE), regardless of recurrence.

It is acknowledged that counting each participant once ignores the number of occurrences or recurrence pattern of an event. If a treatment causes repeated episodes this approach may underestimate the true clinical burden or mask treatment-related patterns.

However, it was considered appropriate in the context of VALIANT, since using a consistent, participant-level count avoids inflated incidence rates that could arise if a few participants experienced repeated events. This helps ensure a fair comparison between treatment groups, especially in smaller studies where repeated events from a single participant could disproportionately skew results.

- e) Due to time constraints in addressing clarification questions, it was not possible to conduct the requested SLR in a robust manner in time for these responses.
- f) Unfortunately, due to time constraints in addressing the large number of clarification requests, it was not possible to incorporate these scenarios into the model. Relevant cost data required to accurately represent AE-related costs, as well as equivalent values for comparison with iptacopan, could not be sourced within the available timeframe. However, given the similarity in the incidence of adverse events across treatments, any incremental cost differences associated with managing grade ≥ 3 AEs are not expected to materially affect the overall model results.

- g) Similar to the response to B19f, due to time constraints, an additional SLR was not able to be performed to assess later stage adverse events. Although, CV events are considered to be events – not necessarily treatment related – that are more apparent in later stages of kidney deterioration. As indicated in response to B19f, given the similarity in the incidence of adverse events across treatments, any incremental cost differences associated with managing grade ≥ 3 AEs are not expected to materially affect the overall model results.
- h) Please see response to B19f.

Health-related quality of life

B 20. Priority question. For CKD stage 1 and 2, utility values were informed by EQ-5D-5L data from the VALIANT study.

- a) **Please discuss the representativeness of the utility values derived from the VALIANT study for the primary C3G as well as primary IC-MPGN patient population differentiating between adolescents aged 12-17 years and adults, considering available literature and other evidence, such as priorly published TAs by NICE or submissions published by other HTA agencies.**
- b) **Please discuss whether the available observation timepoints (i.e., baseline, week 26, week 52) are sufficient to capture the course of the disease, in terms of frequency and duration between measurements.**
- i. **Please discuss the approach to inform HRQoL by data differing periods for pegcetacoplan (52 weeks, including open label period) versus comparators (26 weeks, randomised trial period).**
 - ii. **Please inform HRQoL regressions by the randomised controlled trial period of 26 weeks for both intervention and comparators, and provide a scenario analysis including updated utility values in the health economic model.()**

- c) Please justify pooling CKD stage 1 and 2 instead of keeping them separate, especially since they represent the stages with the highest number of observations.
- d) Please explain the mismatch between the model health states which are stratified by uPCR (<1.5, 1.5-2, 2-3, >3) and eGFR levels, and the regression model which captures solely uPCR levels with different thresholds (<1 (HS1), 1-3 (HS2), >3 (HS3)) as reported in the statistical analysis plan(24) (see also clarification questions B9, B10).
 - i. In CS Table 83, It seems as if uPCR is treated as a binary covariate due to having the same coefficient, despite showing different standard errors. Please confirm whether regression model 6 from the statistical analysis plan (Table 28) has been used.
 - ii. Please align the health economic model and regression model used to derive health state utilities in terms of eGFR and uPCR, and use the observed standard errors from the regression model.
- e) Please provide the source of the algorithm used to map EQ-5D-5L to EQ-5D-3L. If it diverges from NICE health technology evaluations: the manual recommendations(12), section 4.3.16, stipulating the mapping function developed by the Decision Support Unit (Hernández Alava et al. 2017), using the 'EEPRU dataset' (Hernández Alava et al. 2020), please update the health economic model accordingly.
- f) Please discuss the plausibility of the reported, relatively high utility values for the study population in these earlier CKD stages when compared to the UK age- and sex-matched general population utility for the study population (CS health economic model).
 - a) Thank you for your query regarding the utility values. A review of the available literature on patient burden and the impact on HRQoL was conducted as part of the SLR outlined in CS Section .1. Only two studies—Lafayette et al. 2024 and Sidhu et al. 2024—reported on HRQoL using a

generic patient-reported outcome measure. The findings from these studies were previously presented and discussed in the CS.

Overall, patients with C3G had a lower mean utility score compared with the UK general population with the same age/sex characteristics (0.72 vs. 0.90, respectively). Among patients with C3G, those in stage 1 had a mean EQ-5D-5L score of 0.67, while those in stages 4 and 5 had lower scores, averaging 0.58. However, the reported value for CKD stage 1 appears inconsistent, as it is lower than the utility values typically observed for stages 2 and 3.

Utility values derived from the VALIANT trial were considered reliable primarily for CKD stages 1–2, as patient numbers for stages 3–5 in the trial were limited. Notably, the utility values for CKD stages 1–2 in VALIANT were higher than those reported in the literature and even exceeded those of the UK general population. This may be attributed to the relatively good health status and younger age of patients enrolled in the trial.

Detailed results of health state utilities from the trial, stratified by indication and age group, are presented in the table below and compared with the mapped utility values by health state in APPEAR-C3G trial used in recent GID-TA11331 (iptacopan for treating complement 3 glomerulopathy).

Table 64. Health state utilities from VALIANT and APPEAR-C3G trials, stratified by indication and age group

Health state	Utility 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

GID-TA11331 is the only NICE assessment conducted within the last 10 years for the indication of interest. It is important to highlight that the health state utility values used in the economic model presented in the CS are largely consistent with those applied in GID-TA11331.

To our understanding of GID-TA11331, the main concern raised by the EAG regarding the health state utilities related primarily to the low utility values assigned to CKD stage 5+. In a scenario analysis, the EAG specifically focused on utility values post-transplant. It is worth noting that this concern has been addressed in the current CS. The current model includes a more detailed representation of post-transplant patients, with health state utilities varying according to the CKD stage following transplantation.

Due to the limited robust C3G/IC-MPGN specific literature, expert clinical opinion was sought prior to submission and following receipt of clarification questions. The utility values used in the base case economic analysis were consistently considered appropriate representations of the C3G/IC-MPGN patient population.

In discussions with clinical experts following clarification questions, in general it was not suggested that HRQoL would be significantly different between adolescents and adults, beyond the expected changes seen in the general population once accounting for age differences. However, the paediatric clinicians did highlight that the disease, in particular whilst undergoing dialysis, tends to impact adolescents more due to the period in their life and how they are likely to miss out on more things, including education, compared to an adult, which is likely to impact their quality of life.

Table 65 compares the utility values used in previous NICE appraisals for IgAN and C3G with those selected by the Company. As shown, there are notable discrepancies in the estimates, particularly in the later CKD stages. However, prior TAs derived these later-stage values from Cooper et al. (2020), a study based on a general CKD population rather than patients with IgAN, C3G, or IC-MPGN specifically. Clinician feedback prior to submission

suggested that utilities for CKD stages 4 and 5 should be lower across all uPCR levels when compared with the Cooper et al. (2020) values due to a potential for more rapid loss of kidney function, sometimes progressing to ESKD at a younger age, recurrent flares and ongoing inflammation, and higher levels of fatigue. Accordingly, the data from Sidhu et al. and the VALIANT study are considered more representative of the quality-of-life experienced by patients with C3G/IC-MPGN relative to those with CKD, particularly in advanced disease stages.

Table 65: Summary of utility values used in the current and previous NICE TAs

Parameter		TA937	TA1074	GID- TA11331 (unadjusted)	Chosen utility values
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

As reported in TA1074, a 2022 preference elicitation survey by Zhou et al. provides further evidence for IgAN-specific health state utility, segmented by proteinuria level (25). In the survey, utilities were elicited from the UK general population during computer-assisted telephone interviews. Respondents (N=200) were shown nephrologist-validated written vignettes that described several health states for IgAN with different CKD stages, proteinuria levels, and dialysis status, and for a health state with nephrotic syndrome. Utilities decreased with both IgAN CKD stage progression and worsening proteinuria. The relative utility differences between the two proteinuria subgroups were generally consistent with findings from VALIANT (0.06 in VALIANT vs. 0.13–0.06 in Zhou et al. (25)), supporting a meaningful difference in HRQoL between patients with proteinuria levels above and below 1.0 g/day.

Table 66: IgAN health state utility values from Zhou et al. 2022

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

- b) In response to part i, in principle, health state utility values are determined by the health state itself and vary between time periods only if the health state changes. Accordingly, the utility values used in the CS were differentiated solely based on health states, with no additional independent effect of treatment on HRQoL assumed.

The inclusion of HRQoL data from different time periods for pegcetacoplan (52 weeks, including the open-label extension) versus comparators (26 weeks, randomised trial period) was intended to utilise all available measurements from the trial. This approach aimed to increase the number of observations—a critical consideration in the context of a rare disease—and thereby enhance the reliability of the results obtained.

- ii. Table 67 outlines regression analysis outcomes using only randomised controlled data from the first 26-weeks of VALIANT

Table 67: HRQoL regression analysis output using randomised controlled trial period of 26-weeks only

Variable	Estimate	P-value
Intercept	0.7126	<0.01
EQ-5D baseline value	0.3147	<0.01
Age	-0.0024	<0.01
uPCR > 1 g/g	-0.0803	<0.01

- c) Regression analysis was performed to inform impact of low uPCR values on utility and CKD stage was not included in regression analysis. Base values (for uPCR < 1 g/g) for CKD stages 3 to 5 were sourced from Cooper et al. 2020, while values for CKD 1 and 2 stages were based on result from regression analysis (Intercept + EQ-5D baseline values) due to the fact that most patients in VALIANT trial were in CKD 1 and CKD 2 stages. However, CKD 2 utility value based directly from VALIANT trial or values from Cooper et al. 2020 could have been used, as presented below.

Table 68: Estimated utility values for CKD stage 2 from VALIANT and Cooper et al. 2020

	CKD 2 – based on VALIANT	CKD 2 – based on Cooper et al 2020
Stable disease	0.907425001055637	0.85
uPCR <1.0	0.907425001055637	0.85
uPCR 1.0 - 3.0	0.844438664055637	0.787013663
uPCR >3.0	0.844438664055637	0.787013663

- d) Please see response to B9a.
- e) R package eq5d, which has been used to deliver health state utilities refers to three sources for DSU mapping from EQ-5D-5L to EQ-5D-3L:
1. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *Pharmacoeconomics*. 2023 Feb;41(2):199-207. doi:10.1007/s40273022012187. Epub 2022 Nov 30. PMID: 36449173.

2. Hernández-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: The switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. J Health Econ. 2017 Sep;55:139-152. doi:10.1016/j.jhealeco.2017.06.013. Epub 2017 Jul 4. PMID: 28778350.
3. <https://sheffield.ac.uk/nice-dsu/methods-development/mapping-eq-5d-5l-3l>

As such, applied mapping is consistent with NICE guidelines.

- f) Based on expert clinical feedback received both prior to submission and in response to clarification questions, the utility values applied for patients in CKD stage 1–2 with UPCR <1.0 g/g were considered appropriate and consistent with clinical expectations. Experts explained that patients within this subgroup typically experience minimal or no symptoms and, therefore, are expected to have a health-related quality of life (HRQoL) comparable to that of the age- and sex-matched general population. However, experts also noted that these patients continue to require regular clinical monitoring, including hospital or specialist visits, which may contribute to a slightly lower utility value compared with the general population. This is reflected in the model, where the mean utility for patients in this subgroup derived from VALIANT (0.91) is marginally lower than that of the general population reference (0.933 for a 25-year-old, sex-matched to the VALIANT population).

B 21. Priority question. EQ-5D-5L data captured at baseline, week 26 and 52 in the VALIANT study were mapped to EQ-5D-3L. Health state utility values for CKD stages 1 and 2 were estimated using a linear regression model.

- a) **Please provide an overview of the number of HRQoL observations and number of patients at risk per time point, the number and pattern of missingness, and how missing data were handled.**
- b) **Please clarify the reference value used per covariate for all covariates included in the linear regression model presented in the CS Table 83.**

- c) Please argue why a linear regression model is appropriate in this context, compared to a mixed effects model for repeated measures.**
- d) Please explore mixed effects models with repeated measures. Specify in more detail the chosen model (e.g., random intercept/slope) and its fixed and random structure (Tan, Jolani, 2022).(26)**
 - i. Please explore imputation of missing values according to findings in a), considering underlying missing data mechanisms.**
- e) With the mixed effects models mentioned in (d), to investigate the fixed part:**
 - i. Please plot the mean profile of EQ-5D-5L collected from VALIANT over the available time points, differentiated by CKD stage (please also keep CKD stage 1 and 2 separate).**
 - ii. Please justify whether the linearity and normality assumptions are not violated.**
 - iii. Please explain the covariate selection process in more detail, supported by performance metrics such as for instance p-values, F-statistics, and (adjusted) R². Please also report regression models including disease type (C3G, IC-MPGN), eGFR thresholds, and prior/post-transplant as covariates.**
 - iv. Please discuss the relevance of including potential interaction terms.**
- f) With the mixed effects models mentioned in (d), to investigate the fixed part, to investigate the random part:**
 - i. Please explain the selection process of the variance-covariance structure.**
 - ii. Please provide a plot of the subject-specific profiles of EQ-5D-5L collected from VALIANT over the available time points,**

differentiated by CKD stage (please also keep CKD stage 1 and 2 separate).

a) There were 236 EQ-5D observations, from which:

- i. 61 patients with 138 observations for pegcetacoplan
- ii. 58 patients with 98 observations for SOC (52 week excluded).

Missing data included:

- i. 2 incomplete observations (1 SOC patient missing answer for Anxiety/Depression part, 1 pegcetacoplan patient missing answer for usual activity part)
- ii. 12 patients missing EQ-5D measurement at baseline (10 pegcetacoplan patients, 2 SOC patients)
- iii. 36 patients missing EQ-5D measurement at 26 weeks (19 pegcetacoplan, 17 SOC)
- iv. 17 pegcetacoplan patients missing EQ-5D measurement at 52 weeks

No adjustment was made for missing data.

- b) The reference value for all covariates included in the linear regression model presented in CS Table 83 corresponds to the health state utility associated with the reference uPCR category (<1.0 g/g). This reference value aligns with the utility values applied in the model for CKD stages 1 and 2, and the lowest uPCR level, specifically 0.91, which was used in the Company base case.
- c) Linearity assumption was not violated for the model. However, MMRM had shown better fit (based on AIC and BIC) with linear model showing AIC equal to -171.71 and BIC equal to -158.1615, while MMRM with simple variance-covariance matrix shown AIC equal to -245.7 and BIC equal to -228.4.

MMRM models were not considered in the original CS. However, as they appear to fit trial data better than linear regression models, using data from them should be considered.

Table 69: parameters for best fitting MMRM model

Variable	Estimate	Standard error	P-value
Intercept	0.9281959	0.0294512	<0.01
Age	-0.0009941	0.0204978	0.21482
uPCR > 1 g/g	-0.0548361	0.0008014	<0.01

The result from the MMRM did not significantly differ from results of linear regression, therefore changes in utility data are not anticipated to have a substantial impact on model results. Unfortunately, due to time restrictions as a result of the volume and complexity of clarification questions received, it was not possible to incorporate these outcomes into the model.

- d) Since each patient in the VALIANT trial had a maximum of three EQ-5D measurements, imputing missing data was considered likely to introduce substantial bias.
- e) i) Table 70 to Table 75 illustrate the mean profile of EQ-5D-5L collected from VALIANT over the available time points, differentiated by CKD stage.

Table 70: Distribution of answers to EQ-5D-5L questions

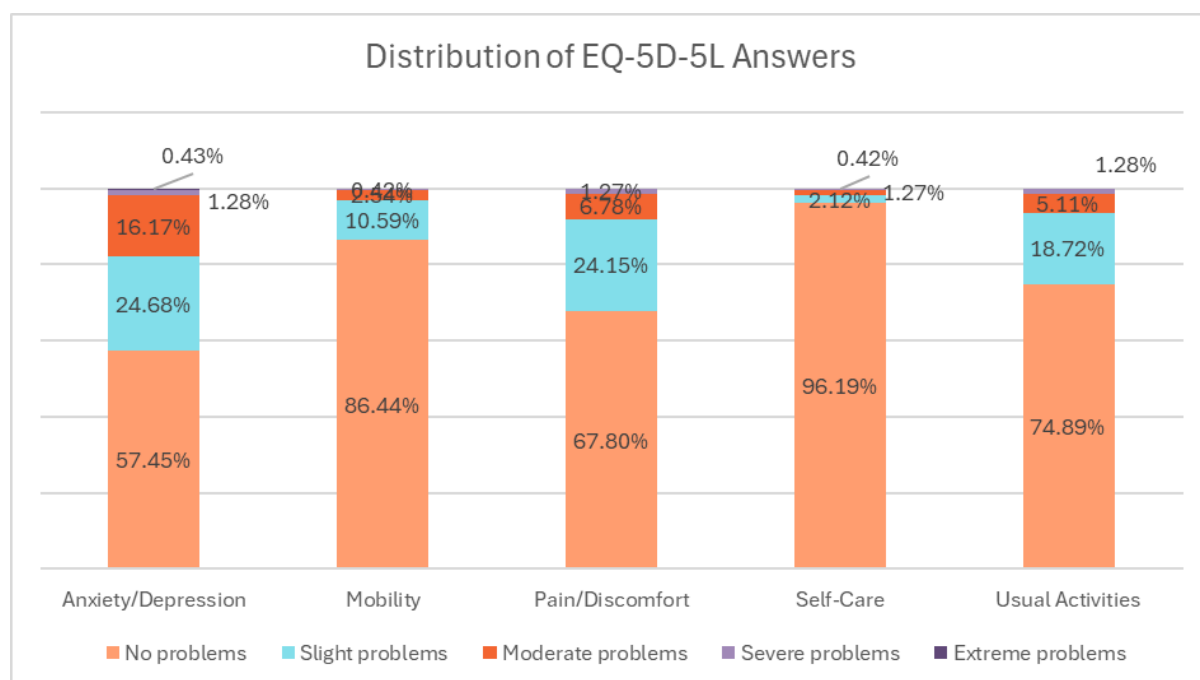


Table 71: Distribution of answers to Anxiety/Depression part of EQ-5D-5L by CKD stage

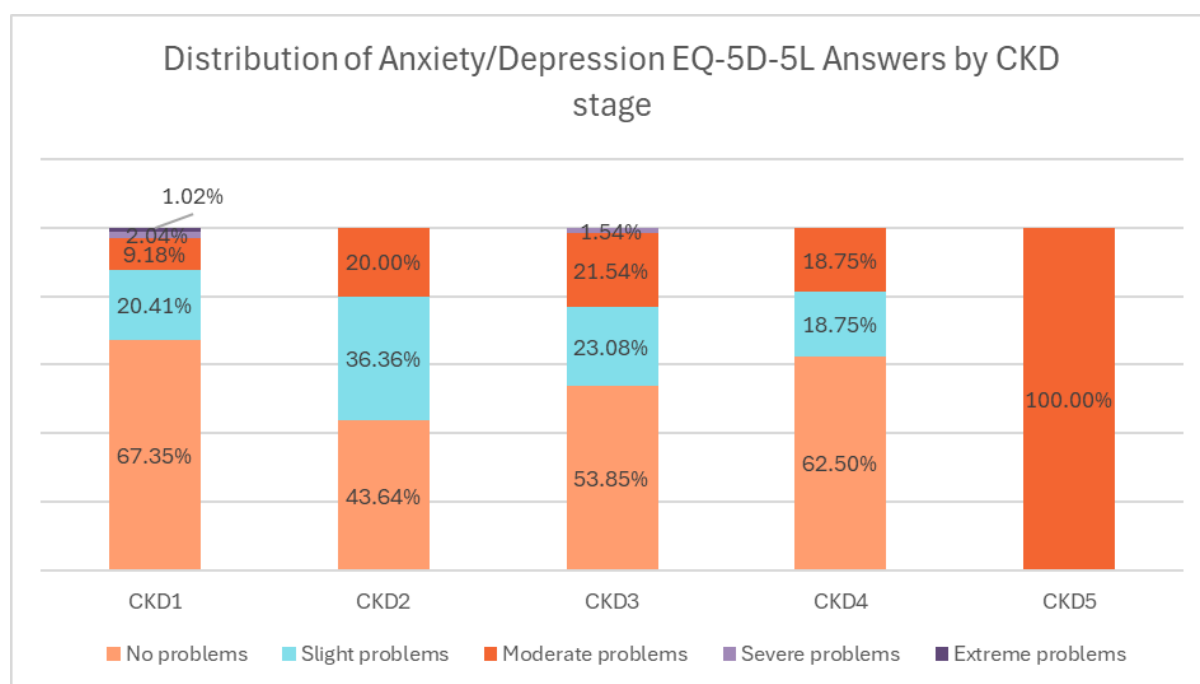


Table 72: Distribution of answers to Mobility part of EQ-5D-5L by CKD stage

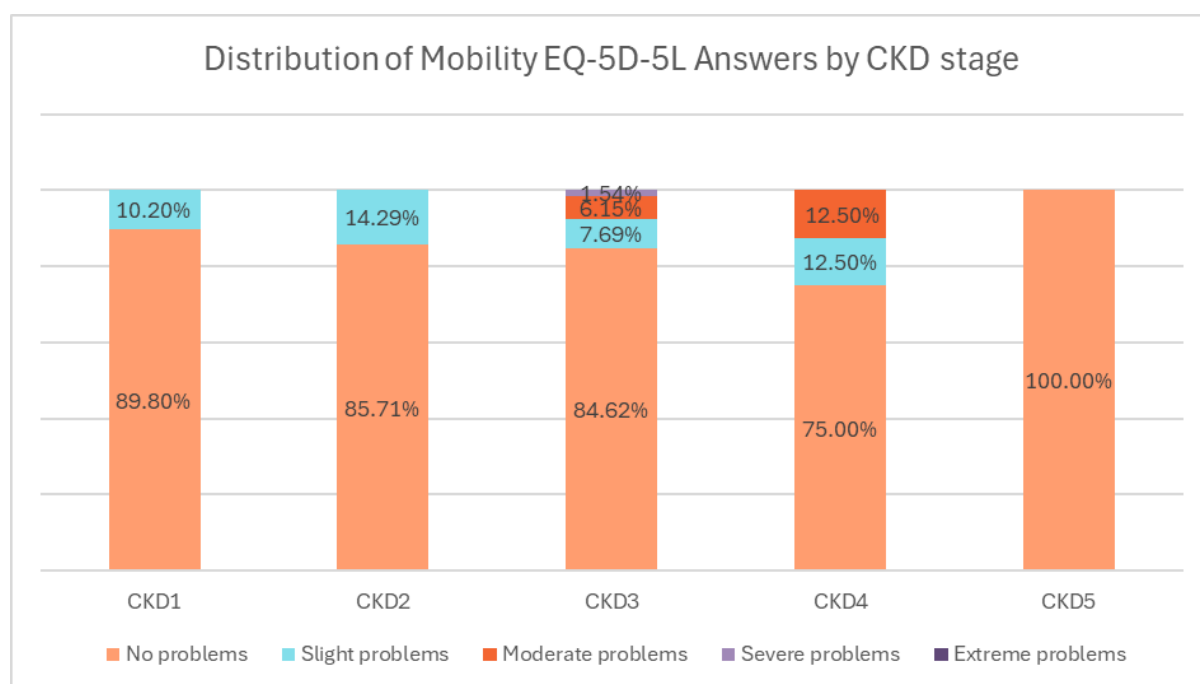


Table 73: Distribution of answers to Pain/Discomfort part of EQ-5D-5L by CKD stage

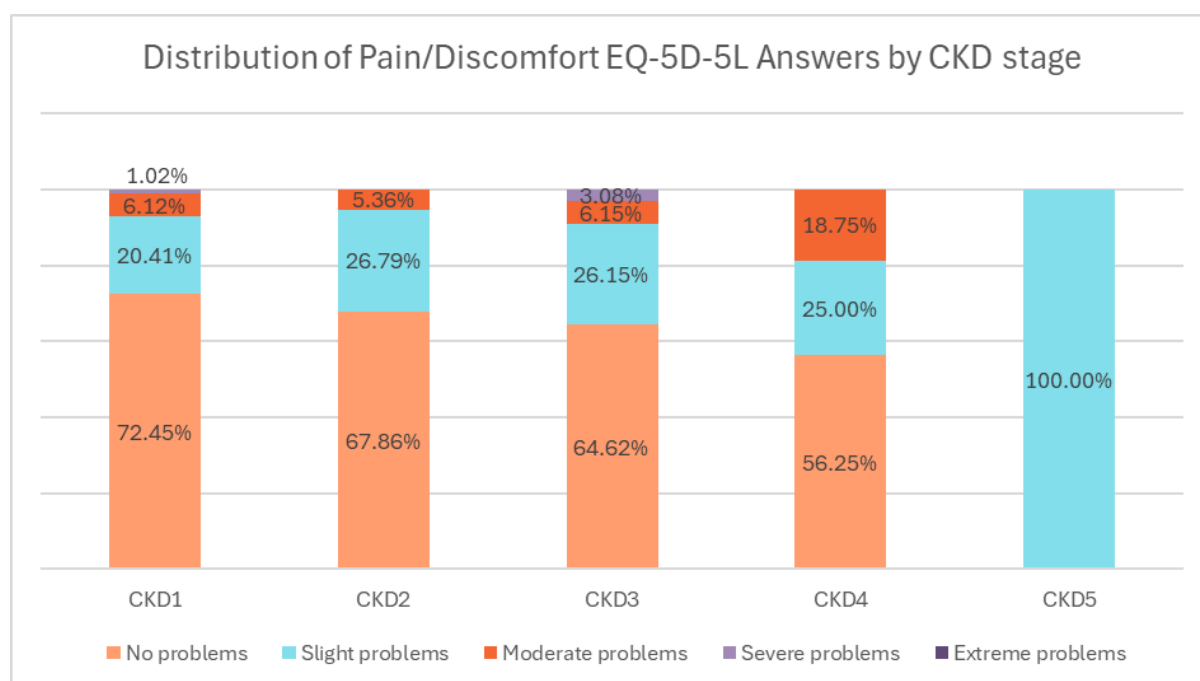


Table 74: Distribution of answers to Self-care part of EQ-5D-5L by CKD stage

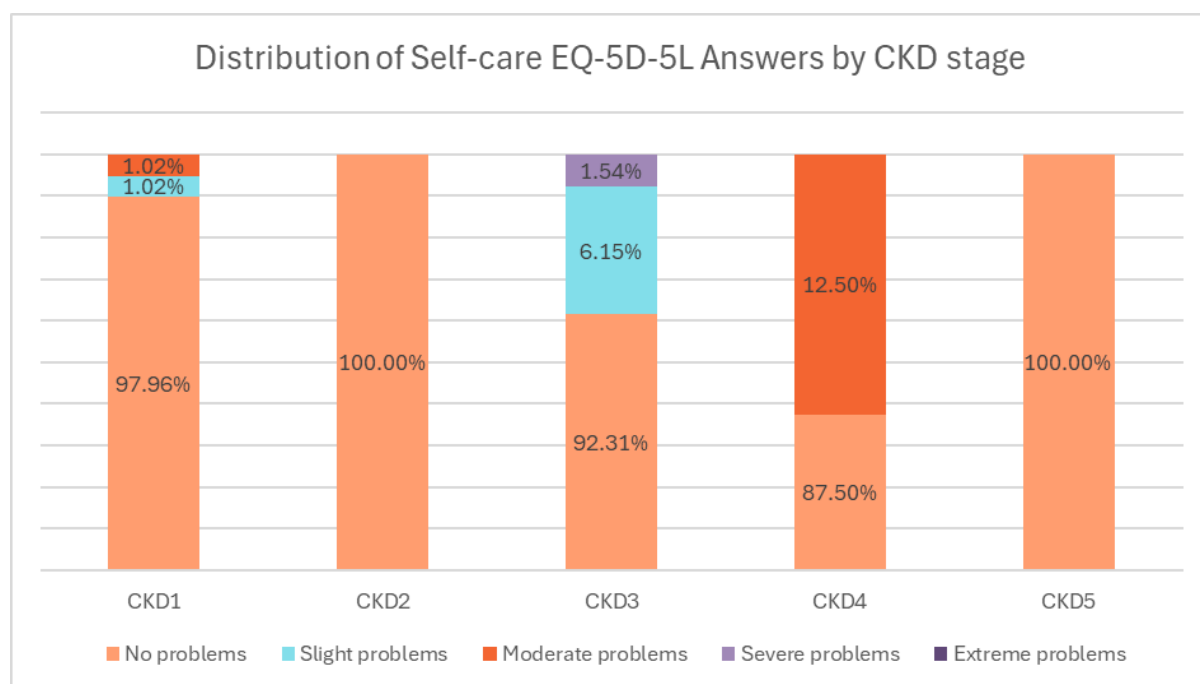
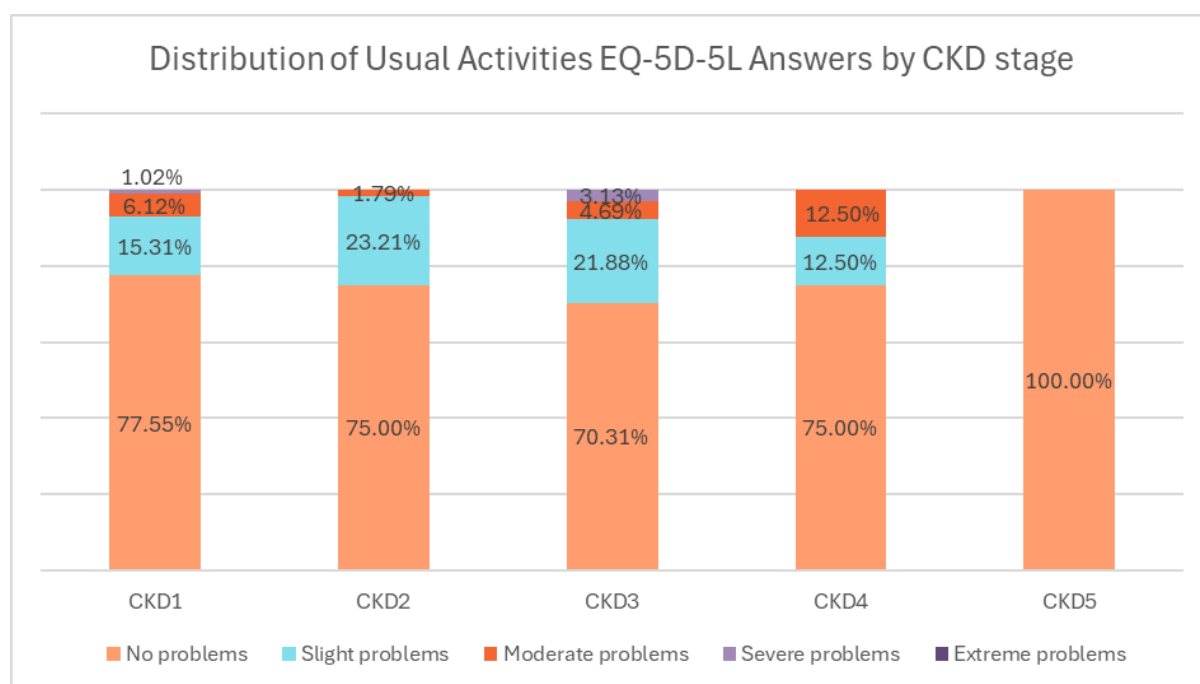


Table 75: Distribution of answers to Usual Activities part of EQ-5D-5L by CKD stage



e)ii) Please see answer to sub-point iii for each MMRM model considered.

e)iii) Based on the model results presented below, inclusion of additional parameters beyond health state (uPCR > 1.0 g/g) and age did not improve model fit. Moreover, the other parameters were not statistically significant. Although a trend was observed for CKD stages 1 and 4 in the MMRM models with an unstructured covariance matrix, these models showed poorer performance according to AIC and BIC compared with those using a simpler variance–covariance structure.

Table 76: Statistics for models with simple variance-covariance matrix

Model variables	AIC	BIC	Shapiro-Wilk normality test (p-value)	Rainbow test for linearity (p-value)	Statistically significant variables
• Age • Health state (uPCR) • Type (C3G, ICMPGN) • Transplant • CKD stage	-240.5	-202.5	Violated (<0.01)	Not violated (1)	Intercept, Health state
•Age •Health state (uPCR) •Transplant •CKD stage	-241.7	-207.2	Violated (<0.01)	Not violated (1)	Intercept, Health state

•Age •Health state (uPCR) •Type (C3G, ICMPGN) •CKD stage	-241.6	-207.1	Violated (<0.01)	Not violated (1)	Intercept, Health state
•Age •Health state (uPCR) •CKD stage	-242.7	-211.6	Violated (<0.01)	Not violated (1)	Intercept, Health state
•Age •Health state (uPCR)	-245.7	-228.4	Violated (<0.01)	Not violated (1)	Intercept, Health state

Table 77: Statistics for models with compound symmetry variance-covariance matrix for visit in correlation to subject ID

Model variables	AIC	BIC	Shapiro-Wilk normality test (p-value)	Rainbow test for linearity (p-value)	Statistically significant variables
• Age • Health state (uPCR) • Type (C3G, ICMPGN) • Transplant • CKD stage	-195.8	-147.4	Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.07042)
•Age •Health state (uPCR) •Transplant •CKD stage	-202.7	-157.8	Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.06878)
•Age •Health state (uPCR) •Type (C3G, ICMPGN) •CKD stage	N/A (convergence problem)		Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.08228)
•Age •Health state (uPCR) •CKD stage	-208.6	-167.1	Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.0811)
•Age •Health state (uPCR)	-229.6	-202.0	Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.05519)

Table 78: Statistics for models with unstructured covariance variance-covariance matrix for visit in correlation to subject ID

Model variables	AIC	BIC	Shapiro-Wilk normality test (p-value)	Rainbow test for linearity (p-value)	Statistically significant variables
• Age • Health state (uPCR) • Type (C3G, ICMPGN) • Transplant • CKD stage	N/A (convergence problem)		Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.06702), CKD1 (0.06841), CKD4 (0.06702)
• Age • Health state (uPCR) • Transplant • CKD stage	-209.1	-157.3	Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.05899), CKD1 (0.06990), CKD4 (0.06844)
• Age • Health state (uPCR) • Type (C3G, ICMPGN) • CKD stage	-207.8	-156.0	Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.07020), CKD1 (0.07009), CKD4 (0.06140)
• Age • Health state (uPCR) • CKD stage	-214.9	-166.6	Violated (<0.01)	Not violated (1)	Intercept, Health state, Trend for Age (0.06983), CKD1 (0.07164), CKD4 (0.06268)
• Age • Health state (uPCR)	-235.3	-200.8	Violated (<0.01)	Not violated (1)	Intercept, Health state, Age

Table 79: Statistics for models with first-order autoregressive variance-covariance matrix for visit in correlation to subject ID

Model variables	AIC	BIC	Shapiro-Wilk normality test (p-value)	Rainbow test for linearity (p-value)	Statistically significant variables
• Age • Health state (uPCR) • Type (C3G, ICMPGN) • Transplant • CKD stage	-186.3	-144.8	Violated (<0.01)	Not violated (1)	Intercept, Health state
• Age • Health state (uPCR) • Transplant • CKD stage	-192.6	-154.6	Violated (<0.01)	Not violated (1)	N/A (convergence problem)
• Age • Health state (uPCR) • Type (C3G, ICMPGN) • CKD stage	-191.5	-153.5	Violated (<0.01)	Not violated (1)	N/A (convergence problem)
• Age • Health state (uPCR) • CKD stage	-197.7	-163.1	Violated (<0.01)	Not violated (1)	Intercept, Health state
• Age • Health state (uPCR)	-218.5	-197.7	Violated (<0.01)	Not violated (1)	Intercept, Health state

e)iv) Due to only health state showing statistically significant impact on EQ-5D, it was considered that interaction terms will not bring improvement for regression.

f) i) As presented in subpoint e) iii. Simple variance covariance matrix has shown the best fit to data (based on AIC and BIC). Additionally unstructured covariance can be considered as it has results with statistically significant age variable and CKD 1 and 4 stages show trend in some models.

f)ii) Please see response to B21e)i)

B 22. Priority question. Health state utility values for CKD stages 3 to 5, as well as for dialysis (haemodialysis (HD), peritoneal dialysis (PD)) and undergoing transplant were informed by literature.

- a) Whereas CS Appendix F addressed the literature review which identified Sidhu et al.'s (2024) study used for CKD stages 3 to 5, CS section 3.4. did not detail SLRs nor appendices pertaining to health state utilities for dialysis or undergoing transplant.**
- i. The CS SLR identified Sidhu et al.'s (2024) and Lafayette et al.'s (2024) abstracts/posters, yet the EAG noted that there are errors in the references, linkage within the text or table (check CS reference 28, 68, 140, 160) as well as data on file (e.g., names: Sidhu 2024 QoL survey.pdf, Sidhu 2024 (abstract).pdf). Please confirm which source informed utility values for CKD stages 3 to 5.**
 - ii. Please provide overviews of the missing SLRs as well as a more detailed SLR for CKD stages 3 to 5 as stipulated by NICE guidance, detailing the inclusion and exclusion criteria, search strategy, identified studies and their results as well as a complete reference lists for included studies and excluded studies and a quality assessment.**
 - iii. Please extend the SLRs not only to published studies but also prior TAs, additionally covering the general CKD population (see for instance, Clarification responses for GID-TA11331, Table 33 and 34 for reference).(27) Additionally, please provide a table of all identified TAs and studies which report HRQoL, specifying the respective CKD variant and mean age of the study population. Please also report utility values and sample size per CKD stage.**
 - iv. Please cross-validate the utility values in the current company base-case with the utility values sourced in b).**
 - v. Based on the cross-validation assessment, please provide an updated economic model and scenario analyses exploring utility values sourced in b).**

- b) Please confirm whether the source populations for literature-based utility values were adjusted to the CS modelled patient population (particularly relevant due to differences, e.g. in age for the general CKD versus CS population), and if not, please do so. Additionally, please discuss the validity of literature-based utility values for the CS patient population, for instance in terms of age-dependent comorbidities.**
- c) Please discuss the representativeness of the study by Sidhu et al. (2024)(28) for the CS utility values of CKD stage 3-5. Please address potential shortcomings and divergences from the NICE scope, for instance the setting, patient population, EQ-5D version, sample size (measurements per CKD stage), eGFR thresholds, and findings on health state values (CKD stage 1 < CKD stage 4 < CKD stage 2 < CKD stage 3a).**
 - i. Please present the number of expected versus observed patients available per time point in Sidhu et al. (2024) to contribute per health state utility estimation, and contrast these to those available in the VALIANT study (for the latter, including stages 3 and 4) in a table.**
 - ii. Please explain the reasoning for applying a uPCR disutility identified in VALIANT to Sidhu et al.'s (2024) measurements. Please also comment on why it is not expected that the impact of uPCR levels may already be reflected in Sidhu et al.'s (2024) utility values.**
- d) Please discuss the assumptions surrounding the kidney transplant utility, particularly the comparability with HD; considering available literature, TAs, and other sources.**
 - i. Please perform a separate SLR on kidney transplant utilities.**
 - ii. Please cross validate the utility values in the current company base-case with the utility values sourced in b).**

iii. Based on the cross-validation assessment, please provide an updated economic model and scenario analyses exploring utility values sourced in b)

a)i) Thank you for bringing this to the Company's attention. These errors arose from two sources, both authored by Sidhu and Lafayette and both published in 2024. The EndNote referencing software appears to have inconsistently selected which author to list first, resulting in this clerical error. This inconsistency also led to the mislabelling of the corresponding "data on file."

References 28, 68, and 140 in the CS refer to *Sidhu R, et al. Self-reported quality of life in complement 3 glomerulopathy patients delineated by CKD stage: a real-world, multi-country survey (29)*, (See "*Sidhu et al (2024)*" in the clarification questions reference pack). This source informed the utility values for CKD stages 3 –5 within the model.

Reference 160 in the CS refers to *Lafayette R, et al. #2632 Quality of life and fatigue burden in individuals living with complement 3 glomerulopathy – a real-world study (30)* (See "*Lafayette R et al (2024)*" in the clarification questions reference pack).

ii) The evidence used to inform utility values from CKD 3 to 5 were sourced from the combined SLR that collected Economic evidence, HRQOL evidence, and costs/HCRU evidence within a single SLR. Although the SLR had a PICO that encompassed all three components, the CS presented 3 adapted versions of the original PICO that includes only Economic, HRQoL and costs/HCRU relevant outcomes in their respective appendices. The inclusion and exclusion criteria, search strategy, identified studies, and their results are all provided within the CS; they can be found in (Table 122, Appendix F), (Table 118, Table 119, Table 120, Appendix E), and (Section F1.2, Appendix F), respectively. No quality assessment was considered for the HRQoL relevant SLR results, as all identified references were congress abstracts/posters. A complete reference list for excluded studies is provided as data on file(31).

iii) To address the component of the question relating to SLRs of health state utilities for patients on dialysis or undergoing transplantation, the HRQoL PICO (appendix F,

table 122) was intentionally defined with sufficient breadth to capture all relevant HRQoL evidence related to C3G and IC-MPGN within these patient populations. This approach ensured that any utility evidence identified for these health states would be representative of the experiences of patients with C3G and IC-MPGN rather than drawn from the broader CKD population.

Due to the limited robust C3G/IC-MPGN specific literature, expert clinical opinion was sought prior to submission and following receipt of clarification questions. The utility values used in the base case economic analysis were consistently considered appropriate representations of the C3G/IC-MPGN patient population.

Table 80 and Table in the company's response to clarification question B20a present a comparison of the utility values used in previous NICE appraisals for IgAN and C3G with those selected by the Company, and changes in health state utility values due to differences in proteinuria from Zhou et al. 2022 as reported in TA1074. The rationale for discrepancies in estimates, particularly in the later CKD stages, is further detailed in the Company's response to B20a.

Utility values for HD and PD align with those used in the previous TAs, but no comparison could be made for utility values used for patients undergoing transplant, as this health state was not used within any previously identified TAs of interest.

As requested, Table 80 identified TAs and studies which report HRQoL, including the respective CKD variant and mean age of the study population. This table also contains the utility values and sample size per CKD stage.

Table 80: Summary of utility values and sample size per CKD stage used in the current and previous NICE TAs

		TA937		TA1074		GID-TA11331 (unadjusted)		Chosen utility values
CKD variant		IgAN		IgAN		C3G		C3G & IC-MPGN
Mean age		64		64		NA		NA
Parameter		Utility	Sample size	Utility	Sample size	Utility	Sample size	Utility
CKD 1	Remission	0.85	29	0.85	29	0.91	394	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	29	0.85	29	0.91	394	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	218	0.80	218	0.86	74	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	423	0.74	423	0.85	16	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	75	0.443	99	0.73	75	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	99	0.451	NA	0.44	99	0.44
PD		0.53	64			0.53	64	0.53
Undergoing transplant		NA		NA		NA		0.44
Post transplant		0.71	209	0.71	209	0.71	209	Same as pre-transplant utilities, by UPCR/CKD stage

iv) Please see response to B20a for a comparison of utility values from the current submission and previous TAs in relevant comparative indications.

v) The updated model has incorporated the utility values identified from the key comparative past and present TAs in Table 80 (TA937, TA1074, GID-TA11331 [adjusting for age/sex]). A summary of these scenarios and the impact on key model results are outlined in Table 81.

Table 81: Scenario analysis - utility values derived from previous/ongoing relevant comparative TAs

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
'New' base case					£35,798	Dominant
Utility from TA937					£38,046	Dominant
Utility from TA1074					£37,829	Dominant
Utility from GID-TA11331 [adjusted values]					£36,908	Dominant

b) Thank you for bringing this to the Company's attention. It is confirmed that the base case did not adjust data from the literature to account for the difference in age between the published source and the modelled cohort. However, this limitation was acknowledged at the time of submission, and the impact of re-weighting the utility values derived from Sidhu et al. to align with the mean age of the model population was explored through a scenario analysis (see Section 3.9.3 of the CS). The results of this analysis indicated a marginal increase in the ICER for pegcetacoplan versus SOC of £401/QALY (£612/QALY in the updated model following clarification). Given that Sidhu et al. was available only as a poster, the level of detail regarding comorbidities was limited, making it difficult to assess the extent to which age-dependent comorbidities may have influenced these utility estimates.

c) As outlined in the CS, the Company prioritised the use of Sidhu et al. to inform utility values for CKD stages 3-5 due to it eliciting responses from C3G patients. However, it is acknowledged that these estimates have limitations, including:

- Analysis included patients beyond just the UK. Specifically, the analysis included responses from patients in the EU5, China, Japan, and US.

- Unlike the NICE reference case, the respondents completed the EQ-5D-5L questionnaire. However, due to lack of granular responses, these responses were not able to be mapped to EQ-5D-3L, as per the NICE reference case.
- Sample size (n=100) is also a limitation identified by Sidhu et al. Due to the rare nature of C3G, sample size is likely to be a regular limitation of such analysis, especially when sub-grouped into different CKD stages where the samples ranged from 13 to 35, depending on the CKD stage.
- The EQ-5D values published by Sidhu et al. used a US based tariff to value responses instead of a NICE preferred UK tariff.

Due to the above limitations, an additional scenario was presented in the original CS which utilised previously used sources for CKD, IgAN and C3G (Cooper et al. 2020) with UPCR based adjustments calculated from VALIANT. This scenario changed the ICER by £2,876/QALY (£3,825/QALY in the updated model),

ci) The Company thanks the EAG for this clarification request. Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to address this point in full at this time. If the issue becomes a priority, it will be considered further, and additional details can be provided if requested.

cii) As reported in response to B20a) both data from VALIANT and Zhou et al have indicated that there is a relationship between UPCR and quality of life. A relationship that was also considered feasible by expert clinical opinion sought prior to the original submission. It was considered that this relationship was independent of CKD stage, therefore it was considered appropriate to apply the UPCR disutility to the estimates from Sidhu et al. As outlined in response to B22b, the characteristics available from the Sidhu et al. poster do not indicate the proteinuria levels of the patients analysed. Therefore, it is difficult to conclusively say whether or not disutility from elevated UPCR values is already captured within these data.

d)i) The Company thanks the EAG for this clarification request. Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to address this point in full at this

time. If the issue becomes a priority, it will be considered further, and additional details can be provided if requested.

d)ii) It is unclear what sources the EAGs question relates to as question b) refers to age adjustments, not identification of new data.

d)iii) As above, it is unclear what sources in b) the EAG are referring to. However, a scenario was explored in the updated model following expert clinical feedback suggesting that the health state utility for patients undergoing a transplant may, on average, be higher than for those receiving haemodialysis (HD). Specifically, clinicians noted that patients may experience lower quality of life than HD recipients during the initial 2–4 weeks following transplant, but gradual improvement would typically be expected over the remainder of the 3-month transplant model cycle, assuming no adverse complications.

In this scenario, it was assumed that patients experienced utility values equivalent to HD for one-third of the model cycle, with the remaining two-thirds reflecting the average post-transplant utility value (0.71) reported in previous comparative TAs (TA937, TA1074, GID-TA11331 [unadjusted]). This produced an average transplant health state utility value of 0.62 ($1/3 \times 0.44 + 2/3 \times 0.71 = 0.62$).

Table 82 indicates this model parameter has minimal influence on the model results, with a change in the ICER (versus SOC) of £302/QALY following an increase in the average transplant utility value.

Table 82: Scenario analysis - Transplant utility value calculated from HD and average post-transplant utility values

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Base case					£35,798	Dominant
Transplant utility value of 0.62					£36,100	Dominant

B 23. The CS stated that disutilities derived from adverse events were implicitly captured in the clinical trial data health state utility values. Yet, adverse event

disutilities stemming from cardiovascular events were incorporated in the economic model.

- a) Please justify why cardiovascular disutilities were modelled despite the assumption that adverse event disutilities would be implicitly captured in VALIANT.
- b) Please discuss the applicability of the chosen sources for cardiovascular related disutilities, also with regards to differences in the patient population.
- c) Please provide a corresponding SLR on published studies and HTA submission as well as other evidence, including but not limited to the broader CKD population besides the CS patient population. Please provide a table of all identified TAs and studies which report adverse event-induced disutilities, specifying the respective CKD variant and mean age of the study population. Please also report disutility values and study sample sizes.
- d) Please cross validate the disutility values in the current company base-case with the disutility values sourced in b).
- e) Based on the cross-validation assessment, please provide an updated economic model and scenario analyses exploring disutilities sourced in b).
- a) Please see responses to B19 which detail why CV events are considered appropriate to include separate to AE events, therefore, why it is also considered appropriate to capture the associated disutilities associated with CV events.
- b) The Company thanks the EAG for this clarification request. Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to address this point in full at this time. If the issue becomes a priority, it will be considered further, and additional details can be provided if requested.

For added additional analysis on this matter, however, the Company have run an additional scenario to illustrate how the inclusion of CV disutility in the model is conservative due to the life extending nature of pegcetacoplan. In

this scenario, CV disutility was removed from the model which resulted in a £622 decrease in the ICER vs SOC ().

Table 83: Scenario analysis - Removal of CV related disutility from the model

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Base case					£35,798	Dominant
Removal of CV related disutility					£35,176	Dominant

- c) The Company thanks the EAG for this clarification request. Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to provide the table of information as requested.

However, instead we have provided as a reference an SLR of utility values in C3G and IC-MPGN conducted by the Company in September 2025, which contains the majority of the information requested (Sobi dof. SLR utility). The SLR reports both utility and disutility values for selected health states (HSs)/events (HEs) typically observed in patients with C3G and IC-MPGN. While the primary focus was on these populations, the review also includes utility values from studies in broader populations where relevant HSs/HEs were reported, including CKD, kidney transplant, and dialysis.

- d) It is unclear from the question what source of disutilities the clarification question refers to as b) relates to the sources already included in the model base case.
- e) Given the questions concerning the source of CV related events, a scenario exploring the total impact of CV events was explored in the updated model by removing CV events. This analysis resulted in slightly favourable results for pegcetacopan given its life years benefit. A summary of results for this scenario are found in Table 14.

Literature searches

B 24. The EAG was under the impression that some (systematic) literature searches had not been reported in the appendices, that searches were seldomly extended to the general CKD population (despite of informative value since little evidence available in the CS population) and that evidence shared by HTA agencies, e.g. TAs submitted to NICE had not been included in the searches generally.

a) Please update the SLRs to include evidence provided by HTA agencies.

Thank you for the opportunity to clarify this point. The economic SLR reported in the company submission did include searches of HTA websites for NICE, SMC, CDA and PBAC. The following terms were used in the searches:

C3 glomerulopathy

C3G

C3 glomerulonephritis

DDD

dense deposit disease

IC-MPGN

immune complex membranoproliferative glomerulonephritis

membranoproliferative glomerulonephritis

MPGN

No relevant HTA submissions were identified.

b) Please review the CS as well as the EAG clarification requests, and provide SLRs where lacking.

Please refer to our response in 24a.

Healthcare resource use and costs

B 25. Priority question. CS section 3.5.3 states that, for pegcetacoplan, no administration costs were included in the model under the assumption that pegcetacoplan is self-administered subcutaneously by all patients. However, CS section 3.2.3 states that pegcetacoplan can be administered by a healthcare professional or administered by the patient or caregiver following proper instructions with a commercially available syringe system infusion pump. As such, the current approach does not include administration costs for patients whose treatment was administered by a healthcare professional, nor does it factor in costs associated with the provision of “proper instructions”, assuming such provision is given by a healthcare professional.

- a) Please provide justification for the modelled approach, provided that this is likely to underestimate the administration costs for pegcetacoplan.**
 - b) Please provide evidence regarding the distribution of patients that receive pegcetacoplan administered by i) a healthcare professional and ii) the patient or caregiver.**
 - c) Please specify the cost of the commercially available syringe system used for self-administration of pegcetacoplan and justify, with supporting evidence, the decision not to incorporate its cost in the economic analyses.**
 - d) Please provide an updated economic model and scenario analysis incorporating administration costs for patients whose treatment was administered by a healthcare professional and the cost associated with providing instructions to the patients whose treatment was self-administered (and cost of the commercially available syringe system, if reasonable to assume that this would not be paid for by the patient).**
- a) Thank you for bringing this to our attention. The rationale for the exclusion of administration costs for pegcetacoplan was the anticipation that those who

initiate treatment are assumed to receive initial training from a specialist nurse, which the model assumed would be provided during a regular hospital appointment. Additionally, patients who self-administer are not assumed to incur ongoing administration costs that are borne by the NHS. Therefore, due to the chronic nature of C3G/IC-MPGN, the small upfront costs associated with training, assumed to be accounted for within a regular hospital visit, were not anticipated to result in significant differences across treatments.

- b) Pegcetacoplan is expected to be self-administered and based upon the experiences in PNH, the Company expect all patients to have the first dose in clinic and self-administered afterwards. The Company are not currently aware of any patient requiring administration to happen in hospital (unless they are in hospital for another reason) for those treated for PNH.
- c) Pegcetacoplan is provided to PNH patients with a company-funded syringe system via a patient support programme. The same arrangement will apply for C3G and ICMPGN. Accordingly, syringe system costs are excluded from the economic analyses, as they are not borne by the NHS.
- d) To align with the methods used in a previous NICE appraisal (TA778) in which pegcetacoplan was indicated for the treatment of PNH, the model was updated to include a one-off cost in the first cycle where patients receiving pegcetacoplan are assumed to receive the following additional training as part of the treatment initiation process, costed using the latest PSSRU Unit Costs of Health and Social Care 2024 Manual:
 - i. 20 minute specialist nurse time for initial dose, band 6 (£62 per hour [including qualifications]).
 - ii. At-home care is assumed for the second and third doses (30 minutes per visit) to check patients are administering correctly (£27 per weekday hour for home care worker)

The inclusion of this one-off administration cost resulted in a minor increase in the ICER compared to the base case (Table 84).

Table 84: Summary of scenario including one-time administration cost

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Base case					£35,798	Dominant
Addition of one-off administration cost					£35,807	Dominant

B 26. CS section 3.3.6 highlights that a constant discontinuation rate of [REDACTED] per model cycle was assumed for pegcetacoplan and iptacopan (the latter due to an absence of real-world data) based on the six patients that discontinued pegcetacoplan during the VALIANT trial.

- a) Please clarify that after pegcetacoplan discontinuation due to CKD stage 5 and dialyses, the standard of care transition probabilities are applied.
- b) Please provide justification and supporting evidence for the assumption of modelling the pegcetacoplan and iptacopan discontinuation rates as constant over time.
- c) Please provide an updated economic model and scenario analyses (informed by external data, expert inputs and/or other TAs within chronic kidney disease) exploring:
 - i. Alternative discontinuation rates
 - ii. Time-varying discontinuation rates
- d) Please provide time to treatment discontinuation analyses based on the VALIANT trial (including Kaplan-Meier analyses, parametric survival analyses as well as exploring the [cumulative] hazard over time and other diagnostic plots consistent with NICE DSU TSD 14).
- e) Please provide an updated economic model and scenario analyses informing treatment discontinuation of pegcetacoplan, iptacopan, and SoC based on parametric survival analyses in d). Include justification for the selected curves.

- a) Thank you for the clarification questions. The Company can clarify that all patients, regardless of treatment received, have the same transition probabilities out of CKD 5 (to dialysis or transplant) or out of dialysis (to transplant).
- b) The Company are aware of known limitations with using a simplified constant discontinuation rate as discontinuation may vary over time due to several factors (e.g. behavioural changes in patients, accumulation of adverse effects over time, fluctuation in symptoms). However, the extent to which these factors are relevant for pegcetacoplan, especially given the lack of data to inform long-term discontinuation rates in C3G/IC-MPGN patients, is unknown. Therefore, in line with committee discussions during the iptacopan appraisal for C3G, the use of a constant discontinuation rate is considered an acceptable simplifying approach.
- c) i) The model has been updated to reflect additional scenarios applying different discontinuation rates from alternative VALIANT analysis (see response to B26d) as well as discontinuation rates used in GID-TA11331

Table 85: Scenario analysis – Constant discontinuation rate from GID-TA11331

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Base case					£35,798	Dominant
Discontinuation rate of 1.57% (GID-TA11331)					£35,939	Dominant

c)ii) Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to incorporate time varying discontinuation rates into the updated model.

- d) Due to the relatively short follow-up period, limited sample size, and the low number of patients who discontinued treatment during the study, time-to-treatment discontinuation analyses were considered to be of limited value and were therefore not performed or included in the original CS.

However, in response to EAG's request, such an analysis has now been conducted, and the results are presented below.

Figure 12: Log cumulative hazard over time

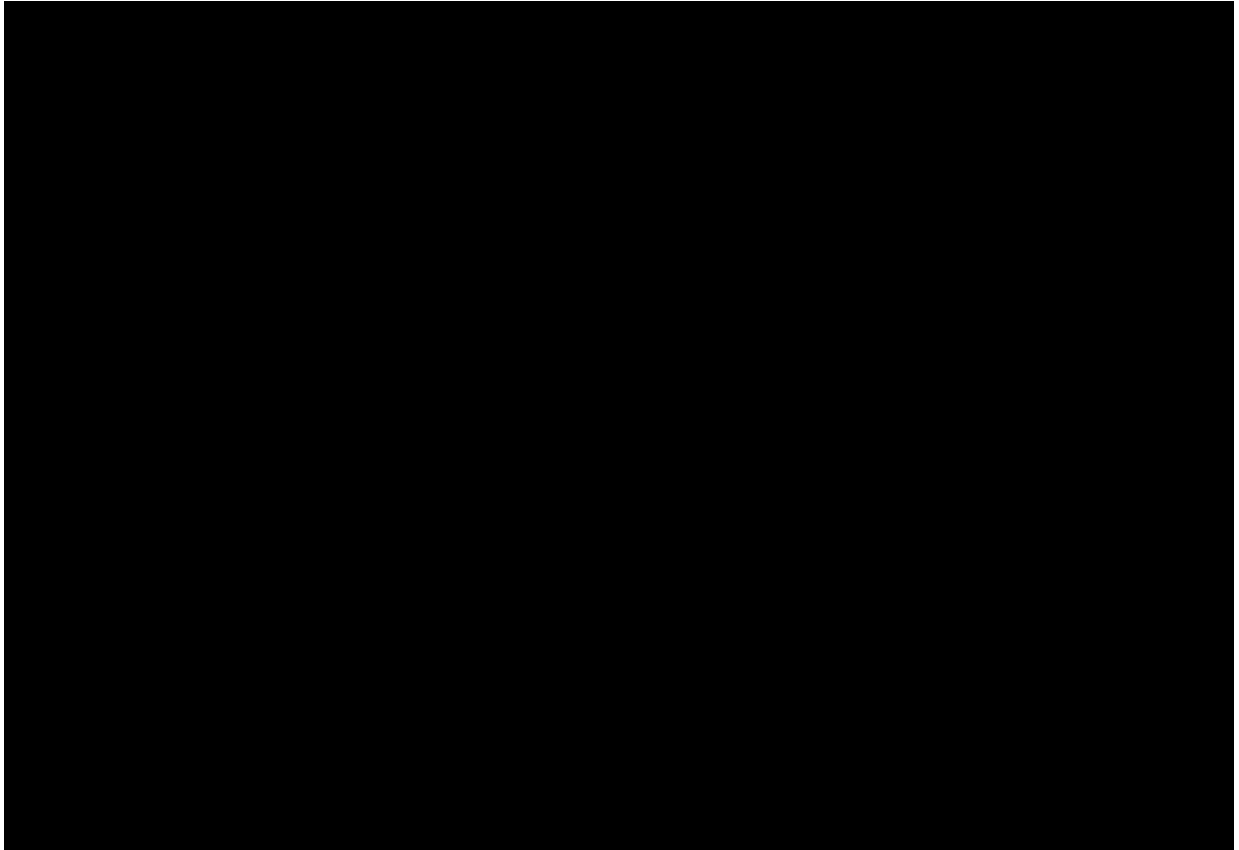


Figure 13: Parametric curves plot

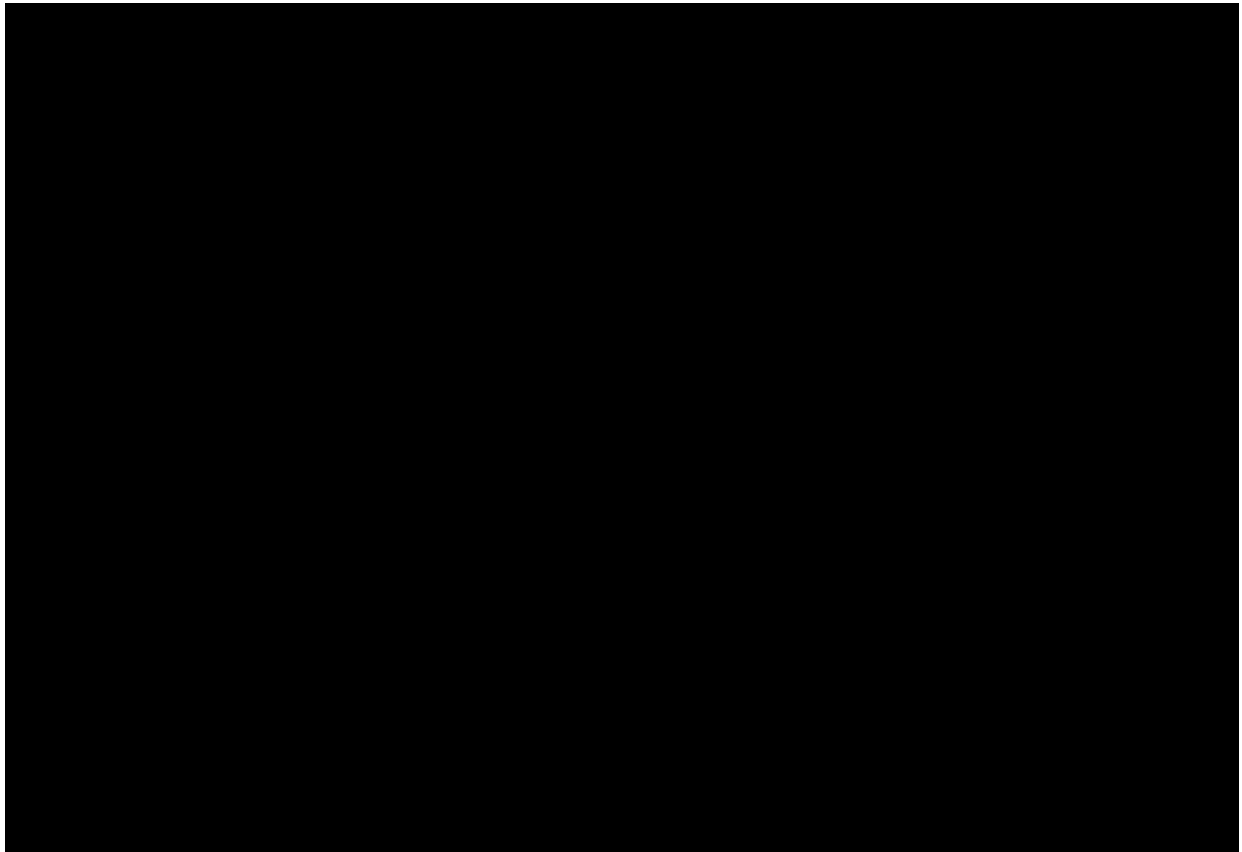


Table 86: Parameters of parametric curves

Parametrization	Parameter 1	Parameter 2	Parameter 3	AIC	BIC
Exponential				-35.27	-35.88
Weibul				-33.27	-34.49
Gompertz				-33.29	-34.51
Log normal				-33.20	-34.43
Log logistic				-33.26	-34.49
Generalised gamma				-31.22	-33.06

e) As previously mentioned, parametric survival analyses are considered to be of limited value in this context. The survival curve plots indicate that all models essentially overlap throughout the study follow-up period.

Nevertheless, based on statistical fit parameters, the exponential model appears to provide the best fit. This aligns with the approach used in the CS, as the exponential model assumes a constant discontinuation rate. However,

the rate estimated from the exponential model differs slightly from that used in the CS, with a value of 1.55% per cycle.

As such, the impact of using this value was explored as a new scenario in the updated model, results of which can be found in Table 87.

Table 87: Scenario analysis - discontinuation rate of 1.55% per cycle

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
Base case					£35,798	Dominant
Discontinuation rate of 1.55%					£35,975	Dominant

B 27. Drug wastage and vial sharing were not clearly discussed within the CS.

- a) Please provide justification and supporting empirical evidence on whether drug wastage and vial sharing are applicable to pegcetacoplan, iptacopan and SoC.
- b) Please provide an updated economic model and scenario analysis incorporating drug wastage and/or vial sharing for the intervention and all comparators. Please utilise a per-pack costing approach for oral treatments in line with NICE guidance.(32)
- a) Thank you for the opportunity to clarify this point. It is anticipated that, given the capsule or tablet formulation of all SOC treatments included in the model, as well as iptacopan, and their use in a chronic treatment setting, drug wastage or vial sharing is unlikely to be a relevant or influencing factor for these therapies.

In regards to pegcetacoplan, the vial size of pegcetacoplan equates to the same required dose for an adult. Therefore, no wastage or vial sharing is anticipated for these patients. For adolescents weighing <50kg, any remaining dose in the vial is expected to be wasted. As such, the model assumes 100% wastage for these patients.

- b) As outlined in response to B27a, no wastage is anticipated for the oral treatments, given their use in a chronic treatment setting. Due to time constraints in addressing the large number of complex clarification questions, it was not possible to incorporate vial sharing for pegcetacoplan. However, as the current model assumes 100% wastage for patients who do not require a full vial, the approach is considered conservative. This is because efficacy outcomes for adolescents are aligned with those for adults in VALIANT; therefore, any potential for lower doses and associated vial sharing would serve only to reduce pegcetacoplan costs within the model.

B 28. 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 before treatment administration. These vaccinations seem not included in the economic model. Further, CS section 3.2.2 suggests that, to achieve disease stabilisation in the model (and consequently temporarily discontinue treatment), a biopsy may be required first. The costs of such a biopsy do not appear to be implemented in the economic model.

- a) Please justify why vaccination costs were not including in the economic model.
- b) Please provide the required administration frequency and corresponding cost of each vaccination and justify the source(s) to inform these.
- c) Please clarify whether patients treated with pegcetacoplan or iptacopan would also likely receive (prophylactic) antibiotics (specify) during treatment and provide justification for their exclusion from the economic model.
- d) Please provide an updated economic model and scenario analysis incorporating the costs associated with the required vaccinations and antibiotics for patients on pegcetacoplan or iptacopan.
- e) Please justify why the economic model did not include biopsy costs for any patients transitioning to the stable disease health state.

- f) Please provide an updated economic model and scenario analysis, incorporating the costs associated with a biopsy for patients transitioning to the stable disease health state.
- a) Thank you for bringing this to our attention. The EAG are correct to highlight that vaccinations against *Neisseria meningitidis* types A, C, W, Y, and B; *Streptococcus pneumoniae*; and *Haemophilus influenzae* type B are required for all patients receiving pegcetacoplan or iptacoplan. Before receiving treatment with pegcetacoplan, in patients with a known history of vaccination, it is ensured that patients have received vaccines against encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and Hib within two years prior to starting pegcetacoplan. If patients have known history of vaccination, the required vaccines are administered at least 2 weeks prior to receiving the first dose of pegcetacoplan.
- b) Table 88 outlines the vaccines and antibiotics provided to iptacoplan and pegcetacoplan patients. This aligns with the assumptions used in the iptacoplan appraisal for C3G (GID-TA1331).

Table 88: Type and frequency of vaccines and antibiotics required for pegcetacoplan and iptacoplan

Vaccines and medications	Proportion of patients	Annual frequency	Unit cost	Cost source
<i>N. meningitidis</i> vaccines	100%	0.2	£105.00	BNF (Bexsero [£75.00] and Nimenrix [£30.00])
<i>S. pneumoniae</i> vaccine	100%	0.2	£49.10	BNF (Prevenar)
<i>H. influenzae</i> type B vaccine	100%	One-off cost	£37.76	BNF (Menitorix)

Penicillin	100%	730.5	£0.03	eMIT (Phenoxymethylpenicillin 250mg tablets). Dosing 250 mg b.i.d.
Total modelled costs				
One-off vaccination cost			£37.76	
Vaccination and antibiotic yearly cost			£52.74	

- c) Thank you for this question. As outlined in response to B28b, costs of antibiotics are also expected to be incurred by patients receiving pegcetacoplan or iptacopan.
- d) The updated economic analysis includes a scenario including the vaccination and antibiotic costs outlined in Table 88. The results of this scenario are available in Table 89 and indicate a minimal impact on the key model outcomes.

Table 89: Scenario analysis - Inclusion of vaccine and antibiotic costs for patients receiving pegcetacoplan or iptacopan

Scenario	Incremental cost		Incremental QALY		ICER vs	
	Standard of Care	Iptacopan	Standard of Care	Iptacopan	Standard of Care	Iptacopan
'New' base case					£35,798	Dominant
Inclusion of vaccine and antibiotic costs					£35,941	Dominant

- e) The Company thanks the EAG for this clarification request. Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to address this point in full at this time. If the issue becomes a priority, it will be considered further, and additional details can be provided if requested.

- f) The Company thanks the EAG for this clarification request. Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to address this point in full at this time. If the issue becomes a priority, it will be considered further, and additional details can be provided if requested.

Results and sensitivity/scenario analyses

B 29. Questions related to the company's base-case and sensitivity/scenario analyses.

- a) The economic model calculates ICERs based on pairwise comparisons of comparators with pegcetacoplan. Please provide an updated economic model and results (deterministic, probabilistic, and scenario analyses) calculating ICERs based on a fully incremental assessment.
- b) The EAG noted the significant differences between deterministic and probabilistic base-case results. Please comment on the reason for the observed differences and provide justification as to the validity of these results. Additionally, please resolve this issue and provide an updated economic model and probabilistic results.
- c) The deterministic one-way sensitivity analysis (DOWSA) excludes baseline/post-transplant distributions of CKD stage and uPCR, uPCR transitions (for intervention/comparators), and probability of CKD5 patients starting dialysis, uPCR distributions after relapse (before and after transplant). Please provide justification for exclusion and provide an updated economic model with DOWSA results including the aforementioned input parameters in the analysis.
- d) Please clarify whether standard errors were utilised as inputs for the PSA, where available and that, where unavailable, standard errors were assumed to be 20% of the deterministic input value. Please highlight any deviations from this approach and provide justification. Please update the health economic model accordingly, prioritising empirical standard errors over approximated ones.

- a) Thank you for this clarification question. The Company can confirm that deterministic fully incremental analysis are available in the model and provided as part of the base case analysis in the original CS (Section 3.8.1). However, this analysis has been expanded in response to the EAG question in an updated economic model with fully incremental results for probabilistic and scenario analyses also.
- b) Thank you for bringing this to our attention. On review of the model, in particular the data used for the PSA, an error was identified in the range at which uPCR transitions were varied in the PSA. This resulted in the range of values used in the PSA being significantly larger than the data would suggest. Correcting this oversight using the bootstrapped standard errors (see response to B9c) provides PSA values that are more aligned with the deterministic outcomes of the model.

	Total		Incremental		Cost-effectiveness	
	Cost	QALY	Cost	QALY	ICER (£/QALY)	NMB (£) at £30,000/QALY
Deterministic result						
Pegcetaco plan	██████	██████	██████	██████	██████	██████
Standard of Care	██████	██████	██████	██████	£35,798	-£39,095
Iptacopan	██████	██████	██████	██████	Dominant	£1,983,971
Probabilistic result						
Pegcetaco plan	██████	██████	██████	██████	██████	██████
Standard of Care	██████	██████	██████	██████	£36,954	-£47,444
Iptacopan	██████	██████	██████	██████	Dominant	£1,978,872

- c) Thank you for highlighting the fact CKD 5 patients starting dialysis parameters were missing from the DOWSA, these have now been added in the latest model version.

Baseline distributions, UPCR transitions, and UPCR distributions were excluded from the DOWSA as by definition varying a single parameter in a distribution would require other parameters to also be varied to ensure they still sums to 100% - no longer making it a OWSA. This makes it difficult to interpret the impact of the change on a single parameter, and impacts on the deterministic results are considered better reflected in a scenario analysis. As such, these sets of parameters were varied within the PSA only.

- d) This is correct, standard errors were utilised as inputs for the PSA, where available and that, where unavailable, standard errors were assumed to be 20% of the deterministic input value.

Validation

B 30. Please specify whether Table 151 of CS Appendix K contains all model input parameters. If not, please provide a complete overview of all model input parameters. Further, for each model input parameter, please specify whether it was included or excluded from the PSA and/or DSA. For all parameter exclusions, please provide justification.

Thank you for bringing this to our attention. Following a review of the parameters provided in Appendix K, one parameter was identified as missing "Proportion of dialysis patients inadequate for kidney transplant". This has now been added to the list of base case inputs alongside clarification as to whether certain parameters were included/excluded from the OWSA and/or PSA, with justifications for any exclusions.

A full list of parameters and justifications for exclusion from OWSA or PSA can be found in the supplementary word document "ID6489 Pegcetacoplan additional response to clarification question B30 - Model parameters and reason for exclusion from sensitivity analysis.docx".

B 31. No cross-validation was provided between the present submission and other relevant technology appraisals. Please provide cross-validations regarding the model structure, modelling assumptions, model inputs (including clinical effectiveness [i.e., time to CKD stage, eGFR slopes, and uPCR],

health state utility values, and resource use and costs), intermediate outcomes, and final outcomes compared with the following previous technology appraisals, in addition to any other relevant TAs identified:

- TA942
- TA937
- TA890
- TA882
- TA877
- TA825
- TA809
- TA807
- TA775
- TA623
- TA599
- TA481
- TA358

Thank you for this question. As outlined in response to B4, only previous appraisals relating to IgAN are considered relevant precedent to which to undertake external validation. Table 90 presents a comparison of key features of the economic analyses from previous NICE appraisals for IgAN and C3G with those applied in the company's submission.

Table 90: Summary of key features of the economic analyses used in the current and previous NICE TAs

Factor	Current submission	TA937	TA1074	GID-TA11331
Time horizon	Lifetime time horizon.	Lifetime horizon (56 years; up to 70 years).	Lifetime horizon (55 years; up to 71 years).	Lifetime horizon (up to age 100).
Cycle length	3-month cycle length.	Monthly (30.4 days).	12-weekly	Aligned with prior CKD appraisals (6 weeks–1 year).
Model structure	Cohort state-transition model	Cohort state-transition model.	Cohort state-transition model.	Cohort state-transition model with CKD1–5 + dialysis/transplant.
Health states (excluding death)	23 health states consisting of three uPCR categories and one stable disease category. Each category is stratified across five CKD stages with an additional four health 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 consisting of three CKD stages (CKD1/2, CKD3, CKD4) for each of four uPCR categories (<0.44 g/g, 0.44–0.88 g/g, 0.88–1.76 g/g, ≥1.76 g/g), totalling 12 states. An additional three states within CKD5 capture pre-RRT, dialysis, and transplant.	Eight health states consisting of six health states representing CKD stages 1–5, two KRT health states (dialysis and post-transplant), and death as an absorbing state
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 (stages 1–4 + dialysis/transplant).
Source of costs	NHS Reference Costs 2023; PSSRU.	NHS Reference Costs 20 21–2022; eMIT; BNF; Kent et al. (2015).	NHS Reference Costs 20 22–2023; eMIT; BNF; IQVIA HCRU report.	NHS Reference Costs; PSSRU; BNF; expert opinion (literature where needed).
Treatment waning effect	No waning assumed.	No waning assumed	Waning applied (sparsentan).	No waning assumed.

Abbreviations: BNF, British National Formulary; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EAG, Evidence Assessment Group; HD, haemodialysis; HCRU, healthcare resource use; IQVIA, IQVIA (data analytics company); KRT, kidney replacement therapy; LTE, long-term extension; NHS, National Health Service; PD, peritoneal dialysis; PSR, Personal Social Services Research; PSSRU, Personal Social Services Research Unit; RRT, renal replacement therapy; SLR, systematic literature review; TA, technology appraisal; UPCR, urine protein-to-creatinine ratio.

B 32. Further external validation of modelled effectiveness would be desirable.

- a) Please report on the face validity of the model structure, modelling assumptions, model inputs, intermediate outcomes as well as final outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).
- b) Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using
 - i. evidence used to develop the economic model.

ii. evidence not used to develop the economic model.

- a) Due to the rare nature of the diseases in question, and the lack of published models in these diseases at the time of submission, external validation of the model structure, inputs, assumptions, intermediate outcomes (e.g. number of transplants) was carried out through expert clinical elicitation in order to ensure any assumptions included in the model passed an initial face validity check. A summary of the validation sought during the model development process is available in Section 3.11.1 of the CS, Appendix L, and Appendix N.
- b) Following the publication of the Committee Papers for iptacopan, key model outcomes have been compared to assess the validity of key model outcomes.

Table 91: Comparison of key discounted model outcomes versus GID-TA11331

<u>GID-TA11331</u>	Total cost	Total LYG	Total QALYs	Incremental LYG	Incremental QALYs
SOC	£355,162	21.11	15.13		
Iptacopan	Redacted	21.59	16.88	0.48	1.74
<u>EAG base case</u>					
SOC	£292,470	-	15.68	-	
Iptacopan	Redacted	-	16.84	-	1.16
<u>Current evaluation</u>					
SOC		21.36			
Iptacopan		22.07		0.71	
Pegcetacoplan		22.73		1.37	

As shown in Table 91, cost and life-year estimates from the two models are broadly consistent. However, QALY estimates for the SOC arms differ slightly, with the pegcetacoplan model predicting lower QALYs than the iptacopan model. One potential explanation is the difference in the number of transplants predicted over a patient's lifetime. In the GID-TA11331 model, SOC patients were estimated to undergo 1.90 transplants and iptacopan patients 1.46, whereas the pegcetacoplan model projected 3.66 and 2.07, respectively. The substantially higher expected number of transplants in the pegcetacoplan model likely contributes to the lower QALY outcomes.

That said, during the GID-TA11331 appraisal, the EAG noted that the model's SOC transplant estimates may underestimate real-world experience. Data from RaDaR indicate that 19% of transplant recipients had already received two or more transplants, despite the relatively young cohort age. This suggests that the true lifetime number of transplants for patients with C3G may exceed 1.9. Clinical experts consulted in response to clarification question B5f also considered the pegcetacoplan model's higher estimate—above three transplants per lifetime—to be plausible, particularly given the high rates of post-transplant disease recurrence in this population.

B 33. The CS section 3.12 states that “validation of the model programming was conducted by secondary health economist to ensure the accuracy of all input parameters and the correctness of the calculations used within the model”.

Please provide further detail regarding:

- a) The tests/checks performed by the secondary health economist and results/outcomes of the performed validation
- b) Please provide complete the TECH-VER checklist() and provide the results.

The Company thanks the EAG for this clarification request. Owing to the complexity and volume of clarification questions received, and the limited time available to respond, the Company was unable to address this point in full at this time. If the issue becomes a priority, it will be considered further, and additional details can be provided if requested

B 34. The EAG noted that loading the economic model and running probabilistic analyses are computationally burdensome.

- a) Please provide an updated economic model improving the loading time when opening the file. Please provide an overview of all changes made to speed up this process.
- b) Please improve the efficiency of macros, particularly for probabilistic analyses. Provide an overview of all changes made.
- a) Following the removal of tunnel health states (see response to B4b), the economic model loading time has been significantly reduced.

- b) Following a review of the macros, it was concluded that the inefficiencies when running any of the scenarios was as a result of the time it took the model to re-calculate. As such, removal of the tunnel states has helped to also significantly reduce (by up to ~50%) the time taken to run the PSA/OWSA/deterministic scenarios.

References:

<https://www.england.nhs.uk/publication/clinical-commissioning-policy-eculizumab-in-the-treatment-of-recurrence-of-c3-glomerulopathy-postkidney-transplant-all-ages/>.
<https://cks.nice.org.uk/topics/chronic-kidney-disease/background-information/prognosis/>.
<https://wwwn.cdc.gov/kdss/detail.aspx?Qnum=Q185>.
<https://www.cdc.gov/acip-grade-handbook/hcp/chapter-7-grade-criteria-determining-certainty-of-evidence/index.html>.

Table 1 outlines all parameters included in the model alongside whether they were included in the OWSA or PSA and a rationale for those that were excluded.

Table 1: Model parameters and reasons for excluding from sensitivity analysis

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Included in OWSA	Included in PSA	Rationale for exclusion
General settings					
Time horizon in years	74	-	FALSE	FALSE	Time horizon is not considered uncertain in the probabilistic sense; it's a modeling choice, not a random variable. Including it in PSA would mix structural and parameter uncertainty
Discount rate for health outcomes [per year]	3.50%	-	FALSE	FALSE	Discount rate is set as preferred by NICE, as such is not considered uncertain
Discount rate for costs [per year]	3.50%	-	FALSE	FALSE	Discount rate is set as preferred by NICE, as such is not considered uncertain
Population					
Age	25.97	23.18 - 28.76: Normal+ (μ,σ)	TRUE	TRUE	
Weight (kg)	63.09	60.46 - 65.72: Normal+ (μ,σ)	TRUE	TRUE	
Male (%)	43.55%	26.48% - 60.62%: Normal+ (μ,σ)	TRUE	TRUE	
Baseline patients distribution in CKD					
CKD 1	45.97%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
CKD 2	20.97%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
CKD 3	29.84%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
CKD 4	3.23%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
CKD 5	0.00%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Baseline patients distribution in uPCR					
uPCR 1	8.87%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
uPCR 2	58.87%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
uPCR 3	32.26%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Treatment - Transplant					
To transplant - from CKD 5 (pegcetacoplan)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
To transplant - from dialysis (pegcetacoplan)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
Re-transplant - from CKD 5 (pegcetacoplan)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	

Re-transplant - from dialysis (pegcetacoplan)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
To transplant - from CKD 5 (soc)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
To transplant - from dialysis (soc)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
Re-transplant - from CKD 5 (soc)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
Re-transplant - from dialysis (soc)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
To transplant - from CKD 5 (iptacopan)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
To transplant - from dialysis (iptacopan)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
Re-transplant - from CKD 5 (iptacopan)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
Re-transplant - from dialysis (iptacopan)	13.45%	8.63% - 19.13%: Beta (μ,σ)	TRUE	TRUE	
Graft survival	95.32%	5.23% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
Graft survival - subsequent transplant	95.32%	5.23% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
Proportion of dialysis patients inadequate for kidney transplant	16.80%	10.75% - 23.87%: Beta (μ,σ)	TRUE	TRUE	
Post transplant CKD distribution					
CKD 1	6.57%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
CKD 2	32.95%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
CKD 3	52.24%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
CKD 4	8.23%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
CKD 5	0.00%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Post transplant uPCR distribution					
uPCR 1		Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
uPCR 2		Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
uPCR 3		Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Treatment - Dialysis					
Probability of CKD5 patients starting dialysis (pegcetacoplan)	100.00%	100.0% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
Probability of CKD5 patients starting dialysis (soc)	100.00%	100.0% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
Probability of CKD5 patients starting dialysis (iptacopan)	100.00%	100.0% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
HD	88.00%	35.84% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
Remission					
Disease remission probability (per cycle) from uPCR1 state - before transplant					
Pegcetacoplan	31.07%	19.61% - 43.84%: Beta (μ,σ)	TRUE	TRUE	

Standard of Care	13.40%	8.60% - 19.06%: Beta (μ, σ)	TRUE	TRUE	
Iptacopan	15.48%	9.92% - 22.01%: Beta (μ, σ)	TRUE	TRUE	
Disease remission probability (per cycle) from uPCR1 state - after transplant					
Pegcetacoplan	31.07%	19.61% - 43.84%: Beta (μ, σ)	TRUE	TRUE	
Standard of Care	13.40%	8.60% - 19.06%: Beta (μ, σ)	TRUE	TRUE	
Iptacopan	15.48%	9.92% - 22.01%: Beta (μ, σ)	TRUE	TRUE	
Probability of disease relapse after remission (per cycle) - before transplant					
Pegcetacoplan	26.00	15.81 - 36.19: Normal (μ, σ)	TRUE	TRUE	
Standard of Care	26.00	15.81 - 36.19: Normal (μ, σ)	TRUE	TRUE	
Iptacopan	26.00	15.81 - 36.19: Normal (μ, σ)	TRUE	TRUE	
Probability of disease relapse after remission (per cycle) - after transplant					
Pegcetacoplan	26.00	15.81 - 36.19: Normal (μ, σ)	TRUE	TRUE	
Standard of Care	26.00	15.81 - 36.19: Normal (μ, σ)	TRUE	TRUE	
Iptacopan	26.00	15.81 - 36.19: Normal (μ, σ)	TRUE	TRUE	
uPCR distribution after relapse -before transplant					
uPCR _1	100.00%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
uPCR _2	0.00%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
uPCR _3	0.00%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
uPCR distribution after relapse -after transplant					
uPCR _1	100.00%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
uPCR _2	0.00%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
uPCR _3	0.00%	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
uPCR transitions					
Pegcetacoplan					
Pegcetacoplan: uPCR1 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
Pegcetacoplan: uPCR1 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Pegcetacoplan: uPCR1 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Pegcetacoplan: uPCR2 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Pegcetacoplan: uPCR2 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Pegcetacoplan: uPCR2 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	

Pegcetacoplan: uPCR3 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Pegcetacoplan: uPCR3 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Pegcetacoplan: uPCR3 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
SoC					
SOC: uPCR1 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
SOC: uPCR1 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
SOC: uPCR1 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
SOC: uPCR2 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
SOC: uPCR2 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
SOC: uPCR2 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
SOC: uPCR3 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
SOC: uPCR3 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
SOC: uPCR3 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Iptacopan					
OR (PEG vs IPT)	████	0.35 - 17.54: Normal (μ, σ)	TRUE	TRUE	
Iptacopan: uPCR1 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	Varying input in the OWSA would require other parameters to also be altered. This makes it difficult to assess the impact of a single model parameter
Iptacopan: uPCR1 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Iptacopan: uPCR1 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Iptacopan: uPCR2 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Iptacopan: uPCR2 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Iptacopan: uPCR2 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Iptacopan: uPCR3 to uPCR1	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Iptacopan: uPCR3 to uPCR2	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
Iptacopan: uPCR3 to uPCR3	██████	Dirichlet_n($\alpha_1, \dots, \alpha_n$)	FALSE	TRUE	
eGFR decline					
Standard of Care (SoC)					
uPCR <1.0	██████	0.8944 - 2.0476: Normal (μ, σ)	TRUE	TRUE	
uPCR 1.0 - 3.0	██████	1.8535 - 4.2435: Normal (μ, σ)	TRUE	TRUE	
uPCR > 3.0	██████	2.8564 - 6.5395: Normal (μ, σ)	TRUE	TRUE	
Pegcetacoplan					
uPCR <1.0	██████	0.0 - 0.0: Normal (μ, σ)	TRUE	TRUE	
uPCR 1.0 - 3.0	██████	0.4315 - 0.9879: Normal (μ, σ)	TRUE	TRUE	
uPCR > 3.0	██████	1.4344 - 3.2840: Normal (μ, σ)	TRUE	TRUE	

Iptacopan					
uPCR <1.0	██████	0.0 - 0.0: Normal (μ,σ)	TRUE	TRUE	
uPCR 1.0 - 3.0	██████	0.4315 - 0.9879: Normal (μ,σ)	TRUE	TRUE	
uPCR > 3.0	██████	1.4344 - 3.2840: Normal (μ,σ)	TRUE	TRUE	
Remission					
eGFR decline in remission	0.0000	0.0 - 0.0: Normal (μ,σ)	TRUE	TRUE	
Global treatment effects					
Discontinuation					
uPCR <1.0	██████	1.07% - 2.35%: Beta (μ,σ)	TRUE	TRUE	
uPCR 1.0 - 3.0	██████	1.07% - 2.35%: Beta (μ,σ)	TRUE	TRUE	
uPCR > 3.0	██████	1.07% - 2.35%: Beta (μ,σ)	TRUE	TRUE	
Adherence with no impact on efficacy					
uPCR <1.0	100.00%	100.0% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
uPCR 1.0 - 3.0	100.00%	100.0% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
uPCR > 3.0	100.00%	100.0% - 100.0%: Beta (μ,σ)	TRUE	TRUE	
Utilities					
CKD 1 - Remission	0.9074	0.3087 - 1.0: Beta (μ,σ)	TRUE	TRUE	
CKD 1 - uPCR 1	0.9074	0.3087 - 1.0: Beta (μ,σ)	TRUE	TRUE	
CKD 1 - uPCR 2	0.8444	0.3915 - 0.9996: Beta (μ,σ)	TRUE	TRUE	
CKD 1 - uPCR 3	0.8444	0.3915 - 0.9996: Beta (μ,σ)	TRUE	TRUE	
CKD 2 - Remission	0.9074	0.3087 - 1.0: Beta (μ,σ)	TRUE	TRUE	
CKD 2 - uPCR 1	0.9074	0.3087 - 1.0: Beta (μ,σ)	TRUE	TRUE	
CKD 2 - uPCR 2	0.8444	0.3915 - 0.9996: Beta (μ,σ)	TRUE	TRUE	
CKD 2 - uPCR 3	0.8444	0.3915 - 0.9996: Beta (μ,σ)	TRUE	TRUE	
CKD 3 - Remission	0.7500	0.4068 - 0.9679: Beta (μ,σ)	TRUE	TRUE	
CKD 3 - uPCR 1	0.7500	0.4068 - 0.9679: Beta (μ,σ)	TRUE	TRUE	
CKD 3 - uPCR 2	0.6870	0.3916 - 0.9149: Beta (μ,σ)	TRUE	TRUE	
CKD 3 - uPCR 3	0.6870	0.3916 - 0.9149: Beta (μ,σ)	TRUE	TRUE	
CKD 4 - Remission	0.5800	0.3470 - 0.7952: Beta (μ,σ)	TRUE	TRUE	
CKD 4 - uPCR 1	0.5800	0.3470 - 0.7952: Beta (μ,σ)	TRUE	TRUE	
CKD 4 - uPCR 2	0.5170	0.3150 - 0.7161: Beta (μ,σ)	TRUE	TRUE	
CKD 4 - uPCR 3	0.5170	0.3150 - 0.7161: Beta (μ,σ)	TRUE	TRUE	
CKD 5 - Remission	0.5800	0.3470 - 0.7952: Beta (μ,σ)	TRUE	TRUE	

CKD 5 - uPCR 1	0.5800	0.3470 - 0.7952: Beta (μ,σ)	TRUE	TRUE	
CKD 5 - uPCR 2	0.5170	0.3150 - 0.7161: Beta (μ,σ)	TRUE	TRUE	
CKD 5 - uPCR 3	0.5170	0.3150 - 0.7161: Beta (μ,σ)	TRUE	TRUE	
HD	0.4400	0.2725 - 0.6149: Beta (μ,σ)	TRUE	TRUE	
PD	0.5300	0.3218 - 0.7328: Beta (μ,σ)	TRUE	TRUE	
Transplant	0.4400	0.2725 - 0.6149: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 1 - Remission	0.9074	0.3087 - 1.0: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 1 - uPCR 1	0.9074	0.3087 - 1.0: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 1 - uPCR 2	0.8444	0.3915 - 0.9996: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 1 - uPCR 3	0.8444	0.3915 - 0.9996: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 2 - Remission	0.9074	0.3087 - 1.0: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 2 - uPCR 1	0.9074	0.3087 - 1.0: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 2 - uPCR 2	0.8444	0.3915 - 0.9996: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 2 - uPCR 3	0.8444	0.3915 - 0.9996: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 3 - Remission	0.7500	0.4068 - 0.9679: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 3 - uPCR 1	0.7500	0.4068 - 0.9679: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 3 - uPCR 2	0.6870	0.3916 - 0.9149: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 3 - uPCR 3	0.6870	0.3916 - 0.9149: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 4 - Remission	0.5800	0.3470 - 0.7952: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 4 - uPCR 1	0.5800	0.3470 - 0.7952: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 4 - uPCR 2	0.5170	0.3150 - 0.7161: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 4 - uPCR 3	0.5170	0.3150 - 0.7161: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 5 - Remission	0.5800	0.3470 - 0.7952: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 5 - uPCR 1	0.5800	0.3470 - 0.7952: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 5 - uPCR 2	0.5170	0.3150 - 0.7161: Beta (μ,σ)	TRUE	TRUE	
Post-transplant - CKD 5 - uPCR 3	0.5170	0.3150 - 0.7161: Beta (μ,σ)	TRUE	TRUE	
Health value of saved kidney					
QALY value of saved kidney	2.4603	1.4959 - 3.4247: Normal (μ,σ)	TRUE	TRUE	
Disutilities					
MI	-0.0580	-0.0353 - -0.0807: Normal (μ,σ)	TRUE	TRUE	
Stroke	-0.1700	-0.1034 - -0.2366: Normal (μ,σ)	TRUE	TRUE	
Heart Faliure	-0.0870	-0.0529 - -0.1211: Normal (μ,σ)	TRUE	TRUE	
Health states costs					

CKD 1 - Remission	£247.80	£160 - £354: Gamma (μ,σ)	TRUE	TRUE	
CKD 1 - uPCR 1	£335.96	£217 - £480: Gamma (μ,σ)	TRUE	TRUE	
CKD 1 - uPCR 2	£495.59	£321 - £708: Gamma (μ,σ)	TRUE	TRUE	
CKD 1 - uPCR 3	£814.87	£527 - £1,164: Gamma (μ,σ)	TRUE	TRUE	
CKD 2 - Remission	£247.80	£160 - £354: Gamma (μ,σ)	TRUE	TRUE	
CKD 2 - uPCR 1	£335.96	£217 - £480: Gamma (μ,σ)	TRUE	TRUE	
CKD 2 - uPCR 2	£495.59	£321 - £708: Gamma (μ,σ)	TRUE	TRUE	
CKD 2 - uPCR 3	£814.87	£527 - £1,164: Gamma (μ,σ)	TRUE	TRUE	
CKD 3 - Remission	£247.80	£160 - £354: Gamma (μ,σ)	TRUE	TRUE	
CKD 3 - uPCR 1	£335.96	£217 - £480: Gamma (μ,σ)	TRUE	TRUE	
CKD 3 - uPCR 2	£495.59	£321 - £708: Gamma (μ,σ)	TRUE	TRUE	
CKD 3 - uPCR 3	£814.87	£527 - £1,164: Gamma (μ,σ)	TRUE	TRUE	
CKD 4 - Remission	£495.59	£321 - £708: Gamma (μ,σ)	TRUE	TRUE	
CKD 4 - uPCR 1	£495.59	£321 - £708: Gamma (μ,σ)	TRUE	TRUE	
CKD 4 - uPCR 2	£1,131.13	£732 - £1,616: Gamma (μ,σ)	TRUE	TRUE	
CKD 4 - uPCR 3	£1,274.09	£825 - £1,820: Gamma (μ,σ)	TRUE	TRUE	
CKD 5 - Remission	£638.55	£413 - £912: Gamma (μ,σ)	TRUE	TRUE	
CKD 5 - uPCR 1	£638.55	£413 - £912: Gamma (μ,σ)	TRUE	TRUE	
CKD 5 - uPCR 2	£1,906.62	£1,234 - £2,723: Gamma (μ,σ)	TRUE	TRUE	
CKD 5 - uPCR 3	£2,049.58	£1,326 - £2,928: Gamma (μ,σ)	TRUE	TRUE	
HD	£8,292.74	£5,367 - £11,845: Gamma (μ,σ)	TRUE	TRUE	
PD	£9,663.08	£6,253 - £13,803: Gamma (μ,σ)	TRUE	TRUE	
Cost of initiating dialysis - HD	£3,520.09	£2,278 - £5,028: Gamma (μ,σ)	TRUE	TRUE	
Cost of initiating dialysis - PD	£1,199.48	£776 - £1,713: Gamma (μ,σ)	TRUE	TRUE	
Transplant	£19,826.92	£12,831 - £28,321: Gamma (μ,σ)	TRUE	TRUE	
Post-transplant	£1,828.18	£1,183 - £2,611: Gamma (μ,σ)	TRUE	TRUE	
Treatment cost					
Pegcetacoplan list price	£80,876.79	-	FALSE	FALSE	The price paid by decision-makers is known. Therefore, drug costs have no associated uncertainty
Standard of Care list price	£210.90	-	FALSE	FALSE	The price paid by decision-makers is known. Therefore, drug costs have no associated uncertainty

Iptacopan list price	£86,420.76	-	FALSE	FALSE	The price paid by decision-makers is known. Therefore, drug costs have no associated uncertainty
Pegcetacoplan discount		-	FALSE	FALSE	The price paid by decision-makers is known. Therefore, drug costs have no associated uncertainty
Standard of Care discount	0.00%	-	FALSE	FALSE	The price paid by decision-makers is known. Therefore, drug costs have no associated uncertainty
Iptacopan discount	0.00%	-	FALSE	FALSE	The price paid by decision-makers is known. Therefore, drug costs have no associated uncertainty
Administration cost					
Pegcetacoplan	£0.00	£0 - £0: Gamma (μ,σ)	TRUE	TRUE	
Standard of Care	£0.00	£0 - £0: Gamma (μ,σ)	TRUE	TRUE	
Iptacopan	£0.00	£0 - £0: Gamma (μ,σ)	TRUE	TRUE	
Cost of health events					
MI	£9,280.00	£6,006 - £13,256: Gamma (μ,σ)	TRUE	TRUE	
Acute stroke	£9,900.00	£6,407 - £14,141: Gamma (μ,σ)	TRUE	TRUE	
Stroke	£371.00	£240 - £530: Gamma (μ,σ)	TRUE	TRUE	
Heart Failure	£4,643.00	£3,005 - £6,632: Gamma (μ,σ)	TRUE	TRUE	
CV - Mortality	£11,382.00	£7,366 - £16,258: Gamma (μ,σ)	TRUE	TRUE	
Renal Death	£11,382.00	£7,366 - £16,258: Gamma (μ,σ)	TRUE	TRUE	
Cost of saved kidney					
Cost value of saved kidney	£256,677.05	£166,108 - £366,639: Gamma (μ,σ)	TRUE	TRUE	
Mortality					
CKD 1	1	0.67 - 1.45: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 2	1.11	0.74 - 1.60: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 3	1.88	1.25 - 2.72: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 4	3.01	2.0 - 4.35: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 5	4.26	2.83 - 6.16: LogNormalX (μ,σ)	TRUE	TRUE	
HD	10.04	6.68 - 14.51: LogNormalX (μ,σ)	TRUE	TRUE	
PD	10.04	6.68 - 14.51: LogNormalX (μ,σ)	TRUE	TRUE	

Transplant	2.5	1.66 - 3.61: LogNormalX (μ,σ)	TRUE	TRUE	
CV events - Stroke					
CKD 1	1.13	0.75 - 1.63: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 2	1.00	0.66 - 1.44: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 3	1.11	0.74 - 1.61: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 4	1.52	1.01 - 2.19: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 5	1.52	1.01 - 2.19: LogNormalX (μ,σ)	TRUE	TRUE	
HD	1.52	1.01 - 2.19: LogNormalX (μ,σ)	TRUE	TRUE	
PD	1.52	1.01 - 2.19: LogNormalX (μ,σ)	TRUE	TRUE	
Transplant	1.52	1.01 - 2.19: LogNormalX (μ,σ)	TRUE	TRUE	
CV events - HF					
CKD 1	1.09	0.73 - 1.58: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 2	1.11	0.74 - 1.60: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 3	1.71	1.14 - 2.48: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 4	2.52	1.68 - 3.65: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 5	2.52	1.68 - 3.65: LogNormalX (μ,σ)	TRUE	TRUE	
HD	2.52	1.68 - 3.65: LogNormalX (μ,σ)	TRUE	TRUE	
PD	2.52	1.68 - 3.65: LogNormalX (μ,σ)	TRUE	TRUE	
Transplant	2.52	1.68 - 3.65: LogNormalX (μ,σ)	TRUE	TRUE	
CV events - CV - mortality					
CKD 1	1.32	0.87 - 1.90: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 2	1.10	0.73 - 1.60: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 3	1.58	1.05 - 2.28: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 4	2.62	1.74 - 3.78: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 5	2.62	1.74 - 3.78: LogNormalX (μ,σ)	TRUE	TRUE	
HD	2.62	1.74 - 3.78: LogNormalX (μ,σ)	TRUE	TRUE	
PD	2.62	1.74 - 3.78: LogNormalX (μ,σ)	TRUE	TRUE	
Transplant	2.62	1.74 - 3.78: LogNormalX (μ,σ)	TRUE	TRUE	
CV events - MI					
CKD 1	1.00	0.67 - 1.45: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 2	1.00	0.67 - 1.45: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 3	1.73	1.15 - 2.50: LogNormalX (μ,σ)	TRUE	TRUE	
CKD 4	2.23	1.48 - 3.22: LogNormalX (μ,σ)	TRUE	TRUE	

CKD 5	2.23	1.48 - 3.22: LogNormalX (μ,σ)	TRUE	TRUE	
HD	2.23	1.48 - 3.22: LogNormalX (μ,σ)	TRUE	TRUE	
PD	2.23	1.48 - 3.22: LogNormalX (μ,σ)	TRUE	TRUE	
Transplant	2.23	1.48 - 3.22: LogNormalX (μ,σ)	TRUE	TRUE	

Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Kidney Research UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the country's leading kidney research charity. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice in the NHS and improve pathways and health outcomes for kidney patients. Our latest annual report 2023/24 shows the majority of our income is from donations, gifts, and legacies. The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are people living with kidney disease and their families.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company,	Sobi - £15,000 Non-commercial projects designed to advance our knowledge of kidney disease, improve prevention and treatment of kidney disease and / or to improve the quality of life for people affected by kidney disease.

Patient organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	To represent the views of patients, we held a focus group with two people living with C3G and the mother (carer) of a teenager with the condition. Because C3G is an ultra-rare condition, there are very few patients and carers who can provide lived experience for this submission.

Living with the condition

Patient organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	People with C3G and their carers reported difficulties with getting a diagnosis in the first place. It took one person with C3G two years to achieve a diagnosis of C3G. Currently in her fifties, she explained: “There were no treatments at that time, so even hearing that there’s a potential treatment is just so exciting. We so rarely hear about anything for us.” She described being put on steroids in her early twenties and being told not to eat anything with protein, salt or sugar, which meant ‘basically anything’. She started dialysis at 26 years old and received a kidney from her mother three years later. “I’ve been very lucky. I’m now 22 years post-transplant and I’ve not had the disease back. “I’ve never had children because there wasn’t enough information about whether I could pass it on.” Another patient currently in her 40s was diagnosed at age 14 years. Because she had been diagnosed relatively quickly and put on blood pressure medication, she successfully delayed progression to kidney failure. About 10 years ago, whilst working in a senior role in London, she was suddenly told she needed a kidney transplant. She underwent a successful transplant (with a kidney donated by her husband) which lasted for about 10 years. She had a second transplant in June last year from a deceased donor and is currently enjoying ‘excellent’ health: “I need to keep my mind strong and have brilliant people around me. I was encouraged not to let my disease stop me and was very lucky with my medical team.” The mother of teenage patient with C3G described the difficulties of getting a diagnosis. Her son first developed symptoms – puffiness around his eyes – at age 10. Then he developed a lump in his neck which would not go away. Finally, he got an appointment with a paediatrician who ran blood and urine tests. The next day, they got a call from the hospital saying they thought her son had nephritis but needed further tests. Her son was tired and grumpy and had lost interest in life; it was hard to know whether this was due to illness or being a pre-teen. She said: “He is currently on the maximum dose of blood pressure tablets and mycophenolate [an immunosuppressant medication] as well. He still has proteinuria but is not classed as a priority for any other treatments. “We don’t want him to need dialysis or a transplant in the near future.

	“This is a challenge for us.” Patients and carers stress that living with C3G is frightening; they face a lot of uncertainty in their lives. One commented: “If and when you get to end stage [kidney disease], you are always thinking ‘please God, let this kidney work’. It’s very frightening.” They also feel alone; the condition is so rare there is ‘no-one else to talk to about this exact thing’. One commented: “We get diagnosed at a very young age. When most of my friends were going out and having fun, I had to stay in and do 24-hour urine samples.” Having C3G can be an embarrassment, particularly for teenagers. The mum remarked: “It’s hard handling the uncertainty and dealing with the sheer number of tests required all the time. We don’t know if it’s getting worse. Plus, all the other things around adolescence. Is it affecting his height etc.? There should be better reassurance and guidance.” One patient commented: “This disease affects you at a young age and will affect you for the rest of your life. Whether you have a good transplant or not, it will still affect you. It impacts your schooling, career choice and where you live. I had to change careers and move house to be near a hospital. It puts you at an economic disadvantage and really contributes to health inequalities.” Another said: “Because it is rapid and aggressive, you can quickly get to end stage. This impacts your relationships. In the ‘90s, my friends were out raving; I was doing peritoneal dialysis. I saw my friends settle down with partners and have babies. At the same time, I was thinking can I survive another month?” For the mum, her son’s diagnosis came as a big shock. She is constantly chasing: “Hospitals are not always great at communication, so I chase for test results, prescriptions and constantly have to follow up in case something gets missed. “Before diagnosis, there’s the early uncertainty. Because you haven’t got a ‘thing’, any single symptom could be serious.”

	School life can be challenging for children with C3G: "I had to go to a parents' evening with a piece of paper to ask every teacher to let him go to toilet and drink water. He's on a low salt diet – so are school dinners suitable? I have to check up on what he's eating. "Different levels of understanding can make it challenging. I need to be on first name terms with school nurse in case anything is going around, such as chicken pox." Carers also experience an impact on their ability to work: "I've turned down job opportunities, because I might need to pivot. So, this also limits my career path." For those patients who have reached kidney failure and have had a kidney transplant, there are other challenges: "We are dependent on medications generally available to transplant patients. Immunosuppression can make you vulnerable to things like COVID. You also need to be aware of longer-term conditions like kidney associated dementia, osteoporosis and other kidney-associated disease."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	All the patients and carers commented upon the inconsistencies of treatment and access to information. One patient remarked: “Patients need access to information and treatment. For example, the regime and experience of having a kidney transplant in London and Glasgow was completely different. “There’s not enough sharing. The US is ahead of the UK. I don’t think this is fair or reasonable. In 2025 there needs to be a better system about what is the best of the best. “With a renal rare disease, you need to become the expert of your own disease. I only know about research trials because I do the research myself. Nephrologists should be clued up and share best practice.” Patients and carers noted that after-care and access to services also need to improve, for example mental health support.

8. Is there an unmet need for patients with this condition?	There are currently no available treatments that target the underlying cause of C3G. Patients want better treatments that are specific for their condition and more research into C3G. They also want access to information and are keen to know their prognosis so that they can plan ahead. One patient explained: “Even if it’s bad, we need clarity so that can plan our lives. We need hope and we need to know the good news as well. “There’s a dearth of information. We don’t even know how many of us there are. Once you know what you are dealing with, you can find information. You really do feel alone. “I just wish there was more research because that immediately gives you hope. When I was in my 20s, I didn’t believe I would get to 35, so now I don’t have a pension. “A cure would be great. We don’t want things to ‘tide us over’; we want medication and better treatments.” The mother added: “We are trying to find a way to control a situation that we have absolutely no control over. Very few people in the UK have gone through this. We’re trying to reassure my son whilst planning for the worst-case scenario. You don’t look down, but you don’t look away. “We have a big wait until ESRD [end stage renal disease]. If there was something that specifically targeted the complement [system], it would make such a difference because he might not need a transplant.” Another patient remarked: “We don’t have another option. Always be mindful that life is precious and short.”

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	• The first advantage and one of the most important is: this gives patients hope.....that may not seem a practical advantage but being told there is no cure, or treatment is devastating for patients. Knowing there is a treatment may help give them a fighting chance • This patient group are mainly children and young adults. The disease can mean needing dialysis and transplant within 5-10 years. Treatment that is specific to C3G has the potential to change this. • Young transplant patients may need several transplants over the course of a lifetime, each transplant exposing them to more antigens and reducing the likelihood of finding a right match the next time – so anything that means it takes longer to reach kidney failure will mean less dialysis and fewer transplants needed over someone's lifetime. • Young people who are living with stage 4 or 5 kidney disease and undergoing dialysis and transplant lose time at school and have reduced training opportunities, leading to inequalities in employment, lifetime earnings etc. A medication that slows progression and improves the health of patients may give young people the opportunity to finish school and training and find better jobs. They may also be less dependent on living close to hospital.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	One patient commented: "I don't see any disadvantages for patients. I appreciate that there will be costs involved in making this available but when you consider the overall costs incurred during the lifetime of one kidney patient being prescribed multiple types of expensive drugs that don't actually tackle the issue, dialysis and in most instances multiple transplants as reoccurrence of this disease happens in half of transplanted patients. I don't think it makes financial sense not to make it available. That's before you start to consider the potential economic impacts on having some of these patients being unable to work and contribute to society and potential mental health-related costs - this is something that must be pushed forward and made available to everyone who needs it."

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Younger patients have more to gain if the treatment prevents disease progression and ultimately the need for dialysis and / or transplantation.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Children are a particularly vulnerable subgroup of patients with chronic kidney disease. The lack of clinical trial data means that they often prevented from accessing new treatments in a timely manner. Kidney Research UK recognises the impact of C3G on underserved communities, as well as those from lower socio-economic backgrounds who do not have good support networks around them.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• C3G is a disease for life. People with the disease want a treatment that is specific to them and will stop progression of the disease, preventing the need for dialysis and transplantation. • Because C3G is an ultra-rare condition, diagnosis is often long and complicated and treatment is inconsistent. People feel very isolated. Accurate and relevant information is hard to find. Living with C3G, or caring for someone with the disease, can be extremely demanding, frustrating and time-consuming. • Having C3G puts people at enormous disadvantages in life. It impacts all aspects of a person's life, from school and education, relationships and having a family, ability to work, choice of career, where you live and, as well as treatment, health and life expectancy. • Even if a patient has a successful transplant, other long-term conditions may affect them later in life. • The mental health-related impact of C3G is significant for people with the disease, their families and friends. Sufficient resources are not available.

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Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	MPGN/DDD Support Group
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	The organisation is a support group for C3G and IC-MPGN patients and offers peer support to its members. Membership is currently 293.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	The organisation has had no funding from the company bringing the treatment to NICE, or any other comparator treatment companies in the last 12 months.
4c. Do you have any direct or indirect links	No.

Patient organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	From conversations with patients and carers. Personal Experiences

Living with the condition

Patient organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with the condition varies from patient to patient, depending on the severity of the disease and its rate of progression to end stage renal failure. For someone with a slow rate of disease progression there might be very little impact on daily life for some years. Whereas for someone who has had rapid disease progression, and is at end stage renal failure, a life on dialysis has a huge impact on daily life. At present in the UK, there is no licensed targeted treatment for these diseases. The diseases are currently managed to try and slow the progression to end stage renal failure and alleviate symptoms. Anxiety and depression are commonly experienced, as knowing you are heading towards a life on dialysis is difficult to come to terms with. Feelings of despondency, lethargy, a 'washed out' feeling, tiredness, headaches, aches and pains, are all commonly experienced by patients. Multiple surgeries await patients of these diseases as they will have to have access lines fitted and removed, fistulas, transplants, feeding portals etc. All surgeries require time in hospital, time spent recovering, pain management and disruption to normal life and activities. Transplanted kidneys sometimes have to be removed due to rejection, infections etc. Complications such as peritonitis, cardiac arrest, and sepsis, are life threatening and often result in lengthy stays in hospital. It is a bleak picture. As well as dealing with the emotional aspects of living with these diseases, there are considerable social implications. Renal decline is associated with poor appetite and dietary restrictions, which makes eating out difficult. Renal meal preparation requires both education and planning. There is an increased cost to patients, both financially and timewise, in buying and preparing renal compliant meals. Not easy when patients are feeling tired, often in pain, and have no desire for food. Fluid restrictions are also a factor for patients and liquid intake needs to be carefully monitored, which makes meeting up and socialising more problematic. Adult patients suffer economic disadvantage as well as carrying an emotional burden. Whilst undergoing dialysis treatment, it can be difficult to maintain a working life due to attending treatment sessions and because fatigue and pain is common. A patient will attend hospital for three sessions a week. Travel time and treatment time typically involve at least six hours out of a day. Patients cannot simply have their treatment and then carry on with their normal activities, as it wipes people out. The treatment itself places a huge physical demand on the body. On top of this, health complications from living with these diseases can lead to multiple hospital admissions, which also makes things difficult with regard to employment. For children, being on dialysis results in educational disadvantage, as school days are missed due to hospital appointments and dialysis sessions. This also has a negative impact on forming friendships. Paediatric dialysis

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	frequently involves more than three sessions a week and the whole day is often taken up by the treatment. This is because the sessions themselves are often of longer duration than for adults and travel time is often longer, due to the fact that there are fewer haemodialysis centres offering treatment to children. Plus the treatment itself leaves children exhausted. Another issue is growth. Children living with kidney disease do not grow as well as healthy children. Dialysis does not improve this situation, so stunted growth amongst kidney patients is common, which can affect self esteem. After time spent on dialysis some patients are considered suitable to have a transplant. The disease frequently recurs in transplants, so patients must deal with not knowing when the disease may strike. This anxiety is made that much worse by the current lack of an effective treatment. Patients feel like they are living under a dark cloud, not knowing how much time they have before they reach end stage renal failure again. It feels like “a ticking time bomb,” as the clock starts ticking. If the patient is a child, then the parent caring for that child is impacted considerably: financially, physically, and emotionally. It can reduce their ability to remain in work because children need a lot of extra care, can spend extended periods in hospital, and need to be accompanied for in centre dialysis treatment. Food preparation, monitoring fluid intake and managing medications, all require time and attention. Carers sometimes administer dialysis treatment at home, whether PD or Home HD. This involves receiving suitable training and a lot of management. Machines have to be prepared, bags of fluid plus ancillary equipment needs to be audited, ordered, stored, and retrieved. There is often considerable sleep disruption overnight as PD machines can alarm many times during the treatment cycles. Quite often, antibiotics need to be drawn up and injected into the fluid bags, which is not a straightforward procedure, but requires great attention and accuracy. For children with PEG tubes, frequently required due to poor appetite and inability to consume enough nutrition, then these too can alarm throughout the night. Considerable time is spent preparing numerous medications to go into the PEG tubes. There is a huge emotional burden for carers, as they will see their children deteriorate over the course of many appointments, procedures, and admissions. When someone has the kidney disease life is disrupted for all the family, especially when the patient is a child. Siblings live with considerable uncertainty in their lives. They never know when a routine clinic appointment might result in their parent being required to stay in hospital with the paediatric patient, often for several weeks. This is because a concerning blood result might require altering treatment regimes, as might a high blood pressure reading. When paediatric patients have home renal replacement therapy, alarms going off during the night disrupts siblings’ sleep and can be a source of worry and concern. As well as facing these issues, siblings

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	frequently have to accompany parents to hospital, alongside the paediatric patients, throughout their school holidays.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	At present these diseases progress to end stage renal failure. There is currently no available treatment to prevent this happening. At best current options delay this inevitability. Treatment for end stage renal failure is either dialysis or a transplant. The disease currently recurs in half of transplanted kidneys at the five year mark, which results in patients needing dialysis treatment or another transplant. Each time a patient is transplanted, antibody sensitivity increases, which results in a smaller pool of potential donors for that patient. This means waiting longer for a suitable donor to be found and spending more time on dialysis. Spending long periods on dialysis is detrimental to overall health and lowers life expectancy for patients.
8. Is there an unmet need for patients with this condition?	Yes. There is currently no available targeted cure for this disease. Some medications might slow down progression to end stage renal failure, but none prevent it.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	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.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None reported.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients are generally treated depending on clinical presentation. In order to have a diagnosis, renal consultants would have been concerned enough to request a biopsy, which would indicate that renal function was compromised. Some of these patients will be managed conservatively, depending on renal function parameters. For patients who are maintaining stable, it could be argued that they might benefit less from the technology than for patients who are not remaining stable. Patients with rising creatinine, and worsening renal function would definitely benefit more from a technology that stopped the disease impairing kidney function. Transplanted patients, who have lost their native kidneys from these diseases, might be another group who would benefit more from the technology than stable patients with the diagnosis. This would be to prevent the loss of the transplanted kidney. Halting the malfunction in the complement system that causes the disease would prevent damage to the kidney. Transplanted patients, who have lost previous transplanted kidneys from these diseases, might be another group who would benefit more from the technology than stable patients with the diagnosis. This could be given prophylactically to prevent the loss of the transplanted kidney. Halting the malfunction in the complement system that causes the disease would prevent damage to the kidney.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equality of access should be taken into account. Patients report differences in their care, such as the time taken to be given a diagnosis. They often feel that the clinicians looking after them lack knowledge and awareness about the complexities of these diseases and they reach out to the support group for more information. A standardised pathway, and oversight from leading experts in the field, would be welcomed by patients.

Other issues

13. Are there any other issues that you would like the committee to consider?	This is an ultra rare disease and this patient group should not be disadvantaged because of this. The numbers in trial data will be lower than for trials for other diseases and this should be taken into consideration and not negatively affect patient access to life changing treatment.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Pegcetacoplan can prevent disease progression to end stage renal failure. • Patient quality of life would improve dramatically without the need for dialysis and transplantation. • Early intervention with pegcetacoplan post transplant can stop the damage to transplanted kidneys. • The introduction of this technology would prevent deaths from these diseases. The complications of these diseases affect heart health, as well as the health of the kidneys, and patients have reduced life expectancy. • Depression and anxiety are already high among young people, exactly the age group that is hit by these diseases. A treatment that offers real hope to the young people affected by these diseases will significantly reduce health related anxiety and depression.

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Patient organisation submission

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Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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About you

Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

1. Your name	
2. Name of organisation	British Association for Paediatric Nephrology
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAPN is an organisation representing health professionals who work with children and young people with kidney disease. It is part of the UK Kidney Association and is funded by subscription from its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes The BAPN has received the following funding from the manufacturer in the past 12 months: £1,500 For a stand at an educational event for paediatric nephrology grid trainees £5,500 To deliver a symposium and package at the PNNG/BAPN annual meeting (PNNG is the paediatric nephrology nurses group) The BAPN is part of the UK Kidney Association (UKKA) which itself has received the following funding from the manufacturer in the past 12 months: £17,000 Corporate membership to UKKA £20,000 For a symposium and stand at UK Kidney Week £120,188 RaDar clinical research – a 12 month contract £180,282 RaDar clinical research - 12 month contract RaDar is a rare renal disease registry that facilitates research into rare kidney diseases which has received support from several pharmaceutical companies

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reverse acute disease To stop progression of disease To prevent end-stage kidney disease
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in proteinuria by at least 50% Reduction in urine protein creatinine ratio to < 100mg/mmol (not possible in all cases) Stabilisation or improvement of eGFR slope References - Masoud et al Kidney International 2025 - Caravaca-Fontan et al Kidney International Reports 2025 - Nester et al Clin J Am Soc Nephrol 2024
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is definitely an unmet need for patients with C3G and IC-MPGN, which leads to an unmet need for healthcare professionals. This is because existing treatments do not address the underlying cause of the disease, have limited efficacy and have significant and debilitating side-effects (such as high dose corticosteroids).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	I will limit my comments throughout this response to the treatment of children and young people (CYP) aged 12-18 years. CYP with IC-MPGN and C3G are treated with a range of agents, depending upon severity of disease. CYP with relatively mild disease (e.g. normal kidney function, low level proteinuria) are generally treated with either ACE inhibitors or angiotensin receptor blockers to provide RAAS blockade. CYP with moderate disease (e.g. moderate proteinuria, mild impairment of kidney function) are treated with high-dose oral corticosteroids and oral mycophenolate mofetil (MMF) in addition to RAAS blockade. If there is a response (e.g. reduction in proteinuria) then corticosteroid dose is generally weaned to low-dose or stopped and MMF is continued, often for 2 years or more, before attempting to wean off. If there is lack of response then immunosuppression is weaned off after several months. In case of lack of response to immunosuppression, CYP are managed by maximising RAAS blockade, using diuretics for oedema and anticipation of the complications of a nephrotic state e.g. thrombosis, infection. CYP with severe disease (e.g. grossly nephrotic state, declining kidney function) are generally managed as an in-patient with IV corticosteroid, followed by oral steroids, a trial of MMF and/or escalation to more powerful immunosuppressive agents such as cyclophosphamide or rituximab. In some cases, regular plasma exchange is attempted as treatment options are exhausted and kidney failure appears inevitable. Children with severe IC-MPGN and C3G will require kidney replacement therapy (ie dialysis) both acutely and/or long-term when end-stage kidney disease develops (ESKD). Kidney transplantation can be performed, although there is a high risk of recurrence and graft loss (ref Obata Transpl Rev 2024). CYP may fluctuate between severity groups over time such that treatment may need escalating and weaning repeatedly during the disease course.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The main guideline currently used in the UK is the KDIGO (Kidney Disease – Improving Global Outcomes) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases – Chapter 8 “Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury”
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The management of CYP with C3G and IC-MPGN has recently been included in the “Clinical practice recommendations for the initial immunosuppressive treatment for children and young people with immune mediated glomerular diseases – a British Association of Paediatric Nephrology/UK Kidney Association harmonisation project”. This is in the final stages of consultation and will be implemented in the coming year. Up until now, the general approach to the management of CYP with C3G and IC-MPGN has been broadly similar across the UK but there has likely been unwarranted variation in terms of dosing and length of corticosteroids and escalation of therapy beyond corticosteroids and MMF. The National Renal Complement Therapeutics Centre in Newcastle provides ad hoc advice to clinicians managing patients with IC-MPGN and C3G in England and Scotland (funded) and to Wales and N Ireland (unfunded).
9c. What impact would the technology have on the current pathway of care?	The results from the clinical trial which have been presented at international meetings are highly encouraging, indicating a dramatic reduction in proteinuria in CYP with C3G and IC-MPGN with pegcetacoplan. In addition the biopsy data showing disappearance of C3 from the kidney biopsy suggest that the root cause of the kidney disease is being targeted. Although the clinical trial did not address the optimal timing of pecetacoplan treatment within the care pathway, I think that it is likely that CYP who receive pegcetacoplan early in their disease course would need less (if any) conventional immunosuppression. I think it is also likely that fewer CYP with C3G/IC-MPGN will require treatment with dialysis following treatment with pegcetacoplan.
10. Will the technology be used (or is it already used) in the same way as current	Most current therapy is administered as oral medication. Pegcetacoplan is administered by twice weekly sub-cutaneous infusion.

care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Most current therapy is administered as oral medication. Pegcetacoplan is administered by twice weekly sub-cutaneous infusion.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Led by tertiary care, in some cases with a shared care arrangement with secondary care (a general paediatrician with a specialist interest in nephrology). There may be benefit of having oversight from a national service to ensure uniformity of access to diagnostic testing and to expedite learning regarding the place of pegcetacoplan in long-term treatment (e.g. understanding who can withdraw from therapy) analogous to the use of C5 inhibition in atypical HUS.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The role of specialist renal histopathologists (and associated technical laboratory support) in the diagnosis of C3G and IC-MPGN is absolutely crucial. Distinguishing between C3G/IC-MPGN and other rare glomerular disorders can be challenging and sometimes requires a second histopathology opinion. In cases where there is diagnostic doubt, use of generic immunosuppression has been a reasonable approach. However now that there is a targeted treatment, the differential diagnosis becomes even more crucial (e.g. exclusion of acute post-infectious GN or paraprotein mediated disease). I think that investment into renal histopathology (for example in a special interest network for discussing cases) would help to direct appropriate use of pegcetacoplan. There will also need to be adequate safety oversight e.g vaccination status, monitoring of infection risk.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Absolutely – yes. Treatment for C3G/IC-MPGN should be aiming for minimal residual proteinuria. Although partial remission of disease achieved by conventional immunosuppression (e.g. significant reduction in proteinuria) has been welcomed, the long term consequences of any residual proteinuria in CYP will have long term impact in terms of kidney survival over a lifetime.

	We do not have head-to-head data of conventional treatment vs pegcetacoplan, however many of the patients in the trial were already on conventional therapy and still met the entry criteria. The trial data suggests impressive reduction in proteinuria. The current immunosuppressive treatments used in children have variable efficacy and significant toxicity. High dose corticosteroids have well-documented negative effects such as hypertension, hyperglycaemia, loss of bone mineral density. However in CYP, the impact on growth and achievement of final adult height, neurocognitive/neuropsychiatric effects and cosmetic effects such as acne and obesity contribute to limited adherence and impaired quality of life. Thus, I think that pegcetacoplan will have better efficacy and reduced toxicity compared with current care.
11a. Do you expect the technology to increase length of life more than current care?	Yes. CYP with ESKD have reduced life expectancy. The expected number of life years lost in children with kidney failure ranges from 16 to 32 years (Wyld JASN 2023).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. CYP with significant kidney disease The quality of life of adolescents starting dialysis (in terms of leisure activities, physical well-being, relationships with friends and energy-vitality score) is lower than in healthy adolescents (Clave BMC Nephrology 2019). I anticipate fewer CYP would need to commence dialysis if receiving pegcetaplan.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In terms of CYP, I don't think so.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There are pros and cons of this comparison Subcutaneous use of pegcetacoplan will require training and ongoing supervision, most likely by specialist nurses. There may also be implications for pharmacy dispensing and disposal of used devices. Some CYP may have procedural anxiety and require some clinical psychology support to access the technology. This is generally available within the paediatric nephrology MDT caring for the CYP. However, some CYP struggle to take their oral medications regularly and would benefit from a supervised twice weekly subcutaneous injection.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I think this is to be determined. I would imagine that a “treat early, save nephrons, withdraw if possible” approach would be ideally suited to this technology, similar to the approach with C5 inhibition and aHUS.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes ESKD has a massive impact on non-health outcomes. The wider impact of a CYP developing ESKD – e.g. on parental employment and mental health, impact on siblings (mental health) and future employment also should be considered. If pegcetacoplan can stop/delay development of ESKD, these are significant benefits which should be explored.

	For children, PedQL can be used to capture quality of life data that includes school functioning. Stories from patients and families with lived experience should be included in the outcome assessment to capture these unmeasured potential benefits. Some references are included below: The significance of relationships and dynamics in families with a child with end-stage kidney disease: A qualitative study - PubMed (nih.gov) Experiences of parents who have children with chronic kidney disease: a systematic review of qualitative studies - PubMed (nih.gov)
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. It is a treatment that targets the underlying cause of the disease. Instead of treating the kidney inflammation that is caused by C3 deposition in the kidneys, it stops C3 deposition in the kidneys. If used early in the disease course, it is likely to change C3G/IC-MPGN from chronic conditions that require intensive follow up and progress to ESKD, to conditions that can be kept quiescent. The focus of management is likely to switch to how long therapy is needed and when it needs to be reinstituted.
16a. Is the technology a 'step-change' in the management of the condition?	Absolutely, yes

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – there are no targeted treatments for C3G/IC-MPGN and this is an entirely unmet need
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Subcutaneous use of pegcetacoplan will require training and ongoing supervision, most likely by specialist nurses. Some CYP may have procedural anxiety and require some clinical psychology support to access the technology. This is generally available within the paediatric nephrology MDT caring for the CYP. Patients will need to be education to be vigilant for specific infections – however they are already in this position when receiving conventional immunosuppression.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction of proteinuria – yes eGFR slope - yes

Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Reduction in C3 deposition in the kidney biopsy was used It is not known if this adequately predicts long term clinical outcomes. However reduction in C3 deposition is very persuasive that the underlying etiology is being treated.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am not aware of any
20. How do data on real-world experience compare with the trial data?	There are limited reports of real world useage, however Mancuso et al report use in five children with C3G (Ped Nephrol 2025). They reported a 70% reduction in proteinuria, and 3 of 4 patients with kidney impairment showed improved kidney function.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes. The clinical trial only included CYP aged 12 years and above. Therefore CYP aged under 12 are not included in this NICE appraisal. CYP aged under 12 years will continue to develop kidney failure from C3G and IC-MPGN whilst older individuals will have the opportunity to access a treatment that may prevent this.
21b. Consider whether these issues are different from issues with current care and why.	Yes – CYP under 12 years of age are currently able to access corticosteroids and MMF

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• C3G and IC-MPGN have a high risk of ESKD and represent an area of unmet need • The lifelong impact of developing ESKD in early life is immense and hard to quantify • The technology is a targeted treatment that represents a step change in management • Early access to treatment will be key to reduce nephron loss, combined with a programme to understand who can withdraw from therapy • Equity of access to diagnostic testing (including histopathology) should be considered

Thank you for your time.

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Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	Renal Pharmacy Group (part of UKKA)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	AMGEN £480 SAMSUNG £ 3,000
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduction in the progression of primary complement 3 glomerulopathy (C3GN) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) to kidney failure requiring dialysis or a kidney transplant.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in proteinuria with a reduction in baseline urine protein creatinine ratio (UPCR). Longer-term, a reduction in the progression of chronic kidney disease (CKD) with a slowing in the rate of decline of estimated glomerular filtration rate (eGFR) and a delay or avoidance of end-stage kidney failure and the requirement for dialysis and/or a kidney transplant.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there are currently no NICE recommended treatments for C3GN or IC-MPGN. Patients usually receive treatment to reduce proteinuria, manage hypertension and to reduce inflammation. Optimised supportive care may include angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARBs) and sodium-glucose co-transporter-2 (SLGT2) inhibitors, in addition to immunosuppressants, including corticosteroids and MMF unless contraindicated.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is currently no specific UK guidance on C3GN or IC-MPGN. The KDIGO 2021 guidelines are utilised. The standard of care is the highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) unless contra-indicated. Second-line therapy can include the use of:

	• Glucocorticoids • Sodium-glucose cotransporter-2 (SGLT2) inhibitors Immunosuppressive agents including mycophenolate can be used to treat rapidly progressing C3GN or IC-MPGN.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The KDIGO guidelines for GN are utilised for the treatment of C3GN and IC-MPGN. There are currently no NICE TAs or UKKA guidelines. There are published NICE Guidelines for the assessment and management of CKD (NG203) however this does not contain specific information on the treatment of patients with C3GN or IC-MPGN.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined from a supportive management perspective with first-line supportive management includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). It is less well defined for second-line therapies and there is uncertainty regarding the efficacy and safety of immunosuppressant drugs in progressive disease and therefore it is recommended that patients are offered the opportunity to be part of a clinical trial. Regional or sub-regional MDTs are recommended for the approval of pegcetacoplan to ensure the drug is being used cost effectively and to ensure equity of access between ICBs.
9c. What impact would the technology have on the current pathway of care?	The technology would be a second-line treatment option for treating C3GN or IC-MPGN in adults, where there is a risk of rapid disease progression, alongside supportive management. Supportive management includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and SGLT2 inhibitors.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be a first-line treatment option for treating C3GN or IC-MPGN in adults, where there is a risk of rapid disease progression, alongside supportive management. Supportive management includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and SGLT2 inhibitors.
10a. How does healthcare resource use differ between the technology and current care?	The technology would be a first-line treatment option for treating C3GN or IC-MPGN in adults, where there is a risk of rapid disease progression, alongside supportive management. Supportive management includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and SGLT2 inhibitors.

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, specialist clinics under a nephrologist.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The ancillaries (pump, syringes) required for administration of the drug are supplied with the drug, however training for the patient to administer the drug via subcutaneous infusion requires taking into account. Specialist nurse and pharmacist time requires investment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, a sustained reduction in proteinuria and resultantly in progression of CKD in individuals with C3GN or IC-MPGN with a delay or avoidance of the need for renal replacement therapy.
11a. Do you expect the technology to increase length of life more than current care?	Yes due to reduced progression of CKD and therefore reduced associated symptoms and complications and also a delay or avoidance of the need for renal replacement therapy.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes due to reduced progression of CKD and therefore reduced associated symptoms and complications and also a delay or avoidance of the need for renal replacement therapy.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no evidence that any specific groups of C3Gn or IC-MPGN patients will respond differently to pegcetacoplan.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The medication is administered via subcutaneous infusion. The pump and syringes required are delivered with the drug and there is a very clear education video to follow for training with patients. However this is time-consuming specialist training required by specialist nurse to ensure patients are safely able to administer the infusion independently at home. No additional monitoring is required over and above what is already undertaken for patients with C3GN and IC-MPGN.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	To be used for patients with a diagnosis of complement 3 glomerulopathy or primary immune-complex membranoproliferative glomerulonephritis. Patients should have had a biopsy for diagnosis prior to treatment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I am not an expert in health economics however I anticipate that pegcetacoplan will improve quality of life for individuals with C3GN or IC-MPGN by reducing or avoiding progression of CKD and associated symptoms as per trial data which will likely be reflected in the QALY calculation.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, it would be the first approved treatment for C3Gn and MPGN. It provides a treatment option which addresses proteinuria which drives progression of the disease.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, this is the first treatment available for the management of C3GN and MPGN.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, currently there are no approved treatment options for the treatment of C3GN or IC-MPGN, a disease often rapidly progressing to end-stage renal failure in young patients, often recurrent after a renal transplantation.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	According to the product literature, the most common adverse effects were injection site reactions and respiratory tract infections. The Valiant trial found that the safety and efficacy of pegcetacoplan was similar to that of placebo treatment (supportive therapy), with low numbers of infection related to pegcetacoplan therapy,

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, all the patients enrolled onto the trial had already received the highest tolerated standard of care treatment (highest tolerated dose of ACE inhibitor or ARB and/or SGLT2 inhibitor), with MMF and corticosteroids permitted as per KIDIGO guidelines and UK practice. Patients had ongoing proteinuria of > 1 g/day and uPCR > g/g in 2 or more first-morning spot urine samples.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important efficacy outcomes are change from baseline in UPCR, the rate of change of eGFR and proportion of patients reaching the composite kidney failure end point. The most important safety outcomes included TEAEs, particularly serious TEAEs or those which led to treatment discontinuation. All of the above outcomes were measured in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	eGFR is used as a surrogate outcome measure for future kidney failure. There is, however, consensus that eGFR slope is highly predictive of future kidney failure risk.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	The real-world practice would reflect that in the Valiant clinical trial with patients in both arms of the trial receiving optimised supportive therapy. The therapy in the comparator placebo arm was reflective of current practice. UK patients also contributed to the studies.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• There are currently no licensed treatments available for C3GN and IC-MPGN. • The presence of proteinuria despite maximum tolerated RAS inhibition and SGLT2 inhibitor therapy has been consistently shown to be a risk factor for progressive decline in renal function in patients with C3GN and IC-MPGN. • Trial data shows a benefit of using pegcetacoplan compared to placebo (supportive therapy) with a reduction in proteinuria and slowed progression of chronic kidney disease • The incidence of treatment emergent side effects was similar with pegcetacoplan compared with the placebo control group. • Pegcetacoplan would be a second-line treatment option to standard care with maximally tolerated RAS inhibition and/or SGLT2is therapy for treating primary C3GN and IC-MPGN.

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Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Professional organisation submission

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About you

Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

1. Your name																		
2. Name of organisation	The UK Kidney Association																	
3. Job title or position																		
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):																	
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.																	
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	<table border="1"> <thead> <tr> <th>COMPANY</th><th>AMOUNT</th><th>PURPOSE</th></tr> </thead> <tbody> <tr> <td>SOBI</td><td>£ 120,188</td><td>RADAR UKKA</td></tr> <tr> <td>ALEXION</td><td>£ 8,500</td><td>EVENTS</td></tr> <tr> <td>NOVARTIS</td><td>£ 275,000</td><td>RADAR</td></tr> <tr> <td>SAMSUNG</td><td>£ 4,250</td><td>UKKA EVENTS</td></tr> </tbody> </table>			COMPANY	AMOUNT	PURPOSE	SOBI	£ 120,188	RADAR UKKA	ALEXION	£ 8,500	EVENTS	NOVARTIS	£ 275,000	RADAR	SAMSUNG	£ 4,250	UKKA EVENTS
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5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no																	

The aim of treatment for this condition 6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	There are key aims of treatment in C3G and IC-MPGN, consistent with many other glomerular diseases. Appropriate timing of biopsy to diagnosis of disease when there is proteinuria and/or decline in kidney function. Early treatment to stop disease activity of C3G and IC-MPGN to minimise development of chronic kidney disease and preserving excellent kidney function. Prevent or reduce progression to kidney failure due to untreated C3G and IC-MPGN and/or development of chronic kidney disease Delay (or prevent) impact of kidney failure to minimise lifetime risk and burden to patients. Prevent or reduce progression to kidney failure due to recurrence of C3G and IC-MPGN following kidney transplant
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Proteinuria is a significant risk factor for kidney failure and reflects active glomerular disease and subsequent chronic irreversible damage. The mechanism for proteinuria reduction reflects the treatment target. It is likely that any sustained reduction in proteinuria reduction can reduce kidney failure risk. Proteinuria reduction as little as 50mg/mmol at 12 months or 20% reduction have been shown to have statistically significant association with risk reduction of kidney failure. Masoud et al KI 2025 10.1016/j.kint.2025.06.003 However the greater the percentage reduction in proteinuria or the lower the amount of proteinuria is likely to associate with greater benefit with complete remission of proteinuria being the ultimate target. Targeting the mechanism of disease is likely to be most beneficial.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Patients with C3G and immune complex MPGN often progress to kidney failure requiring dialysis or transplants. Up to half of prevalent patients have kidney failure. Those who have transplants will often have disease recurrence with graft loss affecting at least a quarter of patients within 3 years. Masoud et al KI 2025 10.1016/j.kint.2025.06.003. Median time to kidney failure estimated to be in the region of 10 years. The average age of diagnosis is around 20 years old. There are high rates of disease recurrence resulting in graft loss due to disease recurrence. As a result, there is considerable lifetime risk of kidney failure in patients with C3G and IC-MPGN in spite of treatments described in section 9. There are no formally approved treatments Up to half of prevalent patients have kidney failure which represents a huge unmet need for patients and healthcare professionals. C3G and IC-MPGN is ultra-rare, affecting 2-4 people per million per year so individual clinicians in secondary renal care may see cases very infrequently resulting in difficulties in disease recognition and management [see 9b on pathways]. Clinical trials address a group of patients with proteinuria and reasonable kidney function [urine P:CR > 100mg/mmol and eGFR>30], however one group who may have even worse prognosis are the group of patients with eGFR<30 have acute inflammatory renal disease, often crescentic who have potential for recovery but were excluded from clinical trials [eGFR<30, rapidly progressive GN].

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Supportive treatments including inhibition of the renin-angiotensin system with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for management of chronic kidney disease due to C3G and IC-MPGN More recently, some clinicians will add in a sodium glucose co-transporter 2 inhibitors (SGLT2i) for management of chronic kidney disease resulting from either C3G or IC-MPGN.

	These treatments only target the resultant damage sustained due to complement activation and inflammation within the kidney. In C3G, If significant proteinuria [proteinuria >1g/day] and/or declining kidney function, immunosuppression with mycophenolate mofetil and corticosteroids. Choice of immunosuppression with mycophenolate and steroids is based on observational data only. In recent years, some patients were enrolled into clinical trials of complement inhibitors instead of starting immunosuppression; others were enrolled into clinical trials of complement inhibitors after inadequate responses following immunosuppression. In refractory cases, clinicians sometimes try other immunosuppression, not limited to cyclophosphamide, rituximab, plasma exchange or eculizumab [Wong et al cJASN 10.2215/CJN.00320121]. These treatments [aside from eculizumab] are not listed in most recent KDIGO guidelines. In IC-MPGN, observational data for choice of immunosuppression is not available but clinicians may choose similar treatments empirically as they would for C3G. In post-transplant recurrent C3G, the high proportion of patients that develop recurrence do so despite immunosuppression that has been commenced as part of transplantation standard of care to reduce risk of allograft rejection. These patients are likely to lose their transplant allografts. In a minority of patients with recurrence, this is aggressive [rapid loss of function, crescents on biopsy] and may be considered for eculizumab under the NHSE clinical commissioning policy 16054/P. Long-term outcomes in those patients who have received eculizumab for this indication appears to be poor based on the experience of the national renal complement therapeutics centre. Therefore long-term outcomes for patients transplanted and develop recurrence are poor with graft loss regardless of whether they are eligible to receive eculizumab or not. Eculizumab is not funded in the NHS for patients without kidney transplants. A similar policy is not available for IC-MPGN. In the EAGLE trial, both C3G and IC-MPGN patients were treated with eculizumab but long-term outcomes were not suggestive of overall benefit of eculizumab in these patients. Ruggenenti et al AJKD 10.1053/j.ajkd.2018.12.046

	Iptacopan is an alternative pathway complement inhibitor working similarly to pegcetacoplan. Phase 3 clinical trials in adults with C3G have been completed and it is undergoing NICE evaluation. Ongoing studies of iptacopan in IC-MPGN and in the 12-17 age group. Other alternative pathway complement inhibitors are being evaluated in clinical trials.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases https://doi.org/10.1016/j.kint.2021.05.015 NHSE Clinical commissioning policy for post-transplant recurrence of C3G. https://www.england.nhs.uk/wp-content/uploads/2017/02/clin-comms-policy-16054p.pdf
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Referral to secondary care is standard for onset of proteinuria, CKD and AKI that are possible clinical presentations of C3G and IC-MPGN C3G and IC-MPGN are some of a few differentials of kidney disease that may be made following kidney biopsy, a routine test in secondary care. If either C3G or IC-MPGN is diagnosed or suspected following initial biopsy review: Clinicians should consider if there is an underlying cause of complement dysregulation - Specialist complement testing may be undertaken. Clinicians should also consider possible secondary causes of C3G or IC-MPGN. The key difference between the two is based on interpretation of immune staining on biopsy. A biopsy favouring IC-MPGN mandates consideration of a wider range of possible secondary causes than in C3G. Many clinicians will refer to expert centres for second opinions especially where uncertainty about diagnosis has been raised. Variation in practice can include: • Threshold for kidney biopsy – ie not enough proteinuria or perception of too much chronic damage to justify biopsy. Failure to diagnose disease could impact future treatment options or consideration of recurrence risks following transplant.

	• Discussion with expert centres [though for patients with recurrent C3G, the NHSE policy focuses referrals to the National Renal Complement Therapeutics Centre for consideration of eculizumab]. • Access to complement testing [eg nephritic factors, anti-FH antibodies, genetics] to look for abnormalities of the complement system that associate with C3G and IC-MPGN. Finding an abnormality can increase confidence of diagnosis and mechanism of action. • immunoStaining techniques in renal pathology vary across England which may make it more difficult to make a diagnosis of C3G or IC-MPGN. • Access to special stains in renal pathology that might reveal key differential diagnosis of C3G eg pronase digest to look for evidence that C3G is due to a paraprotein that requires other treatments,
9c. What impact would the technology have on the current pathway of care?	Clinicians will review prevalent patients who have ongoing clinically significant proteinuria and ongoing risk of kidney failure and carefully assess incident patients who may have a diagnosis of C3G or IC-MPGN. This is in addition to review of incident patients Clinicians may refer a higher proportion of cases than they currently are for specialist review, with a higher need for specialist complement testing and pathology review at an expert centre, to increase confidence of a C3G or IC-MPGN diagnosis or conversely, more confidently exclude a diagnosis of C3G or IC-MPGN prior to considering a complement inhibitor.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is a subcutaneous therapy that is currently being used by some patients within ongoing long-term extension clinical trials and compassionate use in C3G and IC-MPGN. It is already being used in patients PNH. It would be used alongside supportive treatments such as ACEi/ARB in keeping with entry criteria into clinical trials. Clinicians would then likely choose between iptacopan and pegcetacoplan versus mycophenolate or corticosteroids as next line therapies which would reflect clinical trial entry criteria. The absence of controlled data to support the use of mycophenolate and steroids compared to the available data for either iptacopan or pegcetacoplan may influence decision making in favour of an alternative pathway inhibitor. Choosing between iptacopan or pegcetacoplan would be limited to C3G [as best evaluated by the MDT] in adult patients. For patients where the biopsy favours IC-MPGN or in 12-17, the choice would be pegcetacoplan [though trials are ongoing for iptacopan in IC-MPGN].

10a. How does healthcare resource use differ between the technology and current care?	Pegcetacoplan is a subcutaneous infusion whereas supportive care (ACE/ARB) or initial immunosuppression [mycophenolate / steroids] or iptacopan are oral Treatments that are infrequently used and not a significant comparator include Rituximab, cyclophosphamide and eculizumab. These would be intravenous. Plasma exchange would be more intensive and require a vascular catheter, plasma products and nursing expertise to deliver the treatment. Clinical diagnosis and testing as before but potentially a greater emphasis on seeking expert opinion given rarity of disease and less experience of clinicians with C3G and IC-MPGN and complement inhibition. There is also a requirement for vaccinations to mitigate against risk of infection against encapsulated organisms and meningococci.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Initial diagnosis or suspected diagnosis will be made in secondary care but expert opinion or testing may be in specialist centres as per 9b. Once decision to start treatment has been made, prescription of pegcetacoplan would be made by secondary care teams in renal medicine. There may be discussion with expert specialist centres to support diagnosis and also to help assess clinical response.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Consideration of making existing diagnostic tests, clinical expertise more readily available to secondary care in the diagnosis and management of C3G and IC-MPGN. These tests and expertise will not be available in secondary care. Resource will be required to access. Some clinical expertise is resourced in the aHUS service specifications. Cost of complement tests is currently invoiced to referring clinicians. Specifically, in order to increase availability of existing diagnostic tests, it may be necessary to transport biopsy tissue / slides and blood samples for specialist tests to expert centres. Most notably complement testing eg nephritic factors, anti-FH antibodies, genetics that are only available at a single site, the National Renal Complement Therapeutics centre. In addition, some of these blood tests require additional processing at referring centres and transport to diagnostic laboratories on dry ice. Vaccinations for risk mitigation and considering of monitoring of vaccination response.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes

11a. Do you expect the technology to increase length of life more than current care?	Yes. Targeting the underlying mechanism of disease, reduces impact of disease on kidney function and delays time to kidney failure that associates with morbidity and mortality.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Targeting the underlying mechanism of disease, reduces impact of disease on kidney function and delays time to kidney failure that associates with morbidity and mortality.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with acute highly inflammatory disease were excluded from trials due to the acute nature of disease, often with low eGFR in the acute phase of disease. These may have excellent well-preserved kidneys. It is possible these patients have more to be gained if the treatment works in this cohort. Patients with slow indolent decline in kidney function who have pre-existing irreversible kidney disease by the time of diagnosis. These were also excluded from clinical trials and may not benefit as much as other patients. It is possible other subsets of patients with C3G or IC-MPGN with specific complement abnormalities or unrecognised secondary causes may not benefit as much – robust evaluation of treatment outcomes in the real world will help stratify treatment pathways.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Pegcetacoplan is a subcutaneous infusion and requires healthcare staff to administer. There is need to consider risks of infection [mandatory vaccination against pneumococci, haemophilus influenzae type b and also meningococci], patient vigilance and consideration of additional prophylactic antibiotics.

Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Monitoring of clinical parameters would be standard as per starting any therapy however measuring effect of pegcetacoplan on the complement system may require additional tests compared to current standard of care including some samples that require transport to specialist labs using dry ice.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. Review of clinical parameters and biopsy as a minimum to start treatment. Robust exclusion of secondary causes of C3G and IC-MPGN. Evaluation of the complement system would increase confidence of a complement-mediated process. Treatment would be stopped patient if progressed to kidney failure. Other reasons for stopping may be considered if treatment not thought to be effective eg no impact on progressive kidney failure or failure to regulate the complement system. Collection and review of post-treatment would be valuable in stratifying clinical response that may help justify additional stopping criteria and potentially help redefine starting criteria. A programme of research to explore additional stopping criteria including in patients who initially benefit could help determine optimal treatment duration. For example, robust detection of specific abnormalities that dysregulate complement that if no longer present, may mean complement inhibitory therapies such as pegcetacoplan are no longer required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patients with nephrotic syndrome might reduce proteinuria sufficiently to have non-nephrotic range proteinuria. This would lead to improvements in symptomology and reduced risk of complications of nephrotic syndrome that include oedema, risk of infection and thromboembolic events.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. As per 16a and 16b.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. Pegcetacoplan inhibits the alternative pathway of complement which is part of the underlying disease mechanism in C3G and IC-MPGN. It therefore provides a specific targeted for these patients. It demonstrates statistically significant reduction in proteinuria, in a double-blinded randomised control trial over and above current standard of care. Strictly speaking, it is the same step change that iptacopan makes for C3G which is also undergoing evaluation – but pegcetacoplan due to its inclusion criteria in its pivotal trial does provide a further step change in a broader patient group – notably adolescents and IC-MPGN.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. There is therefore a high burden of kidney failure in patients with C3G which represents a huge unmet need for patients and healthcare professionals. Pegcetacoplan reduces proteinuria by targeting the mechanism of action in disease. This is supported by the reduction in C3 staining on biopsy. The outcome is preserving kidney function and at worst delaying

	and at best preventing kidney failure, depending upon the extent of any irreversible damage that has been sustained at the point of starting treatment. In patients who have already reached kidney failure and require dialysis, the mechanism of action in disease is comparable so treatment following transplant will likely reduce the impact of C3G or IC-MPGN on the renal allograft. The effect of pegcetacoplan has been studied in post-transplant patients in clinical trials though numbers are small compared to the number of patients included in trial who have not had a transplant.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Based on the safety data reported in the phase 2 and phase 3 clinical trials of pegcetacoplan in C3G and IC-MPGN, pegcetacoplan appears to be well-tolerated. Due to the mechanism of action of pegcetacoplan, there is likely to be a higher risk of infection due to encapsulated organisms and meningococci. As part of the clinical trials, there is a vaccinations schedule to help mitigate risk of infection. In the clinical trials, only a small number of patients have had infections due to encapsulated organisms and were treated with antibiotics

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes in so far as there is a prevalent cohort of patients with C3G and IC-MPGN in the UK who have ongoing proteinuria [typically urine P:CR >100mg/mol] and eGFR >30/min. These are the patients who were selected for clinical trials of complement inhibition in UK. Patients who have less proteinuria are likely to be at lower risk of kidney failure.

	However, patients with eGFR <30 fall into two categories – those who have significant chronic kidney disease in whom we wouldn't routinely offer immunosuppression currently and who were not included in trials. The group of patients with eGFR<30 have acute inflammatory renal disease, often crescentic who have potential for recovery but were not eligible for clinical trials. There would be an ongoing unmet need in this group. Trials of pegcetacoplan also include patients who have been transplanted with clinical evidence of recurrence and would also reflect UK practice. A minority of patients with rapid decline in graft function would have been excluded from trials but were subject to the eculizumab policy instead.
18a. If not, how could the results be extrapolated to the UK setting?	Under 12 years of age would have been excluded from trials. For post-transplant recurrence, there are patients in UK with under the proteinuria threshold who should also be considered high risk patients. Consideration should be given to treatment of these patients also.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Proteinuria reduction, stabilisation of eGFR demonstrate clinical impact. Improvements in serum C3, reduction in C3 staining on biopsy and reductions in disease activity on biopsy help infer mechanism of action. All were measured in the trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Proteinuria reduction is being shown to associate with stabilisation of eGFR and lower rates of kidney failure.

	Reduction in proteinuria of 30% at 6 months associates with slower eGFR decline and lower rates of kidney failure Caravaca-Fontan et al KI reports 2025. https://doi.org/10.1016/j.ekir.2025.01.024 Reduction in proteinuria of 20% associated with lower kidney failure risk Masoud et al KI 2025 10.1016/j.kint.2025.06.003.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real-world experience largely reflects compassionate use. There are limited reports including in younger patients as reported in 5 patients in Mancuso et al DOI: 10.1007/s00467-025-06673-w These patients had similar outcomes to the ones reported in the phase 3 trial and suggest that the treatment was well tolerated.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	No

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• C3G and IC-MPGN have a high unmet need with high rate of progression to kidney failure despite currently available treatments • C3G and IC-MPGN have a high unmet need amongst patients who require, or have had a kidney transplant. • Pegcetacoplan demonstrates clinically significant reduction in proteinuria as shown in the phase 3 randomised control trial that is likely to reduce long-term rates of kidney failure. • The clinical trial population from available phase 2 and phase 3 data fairly reflects the C3G and IC-MPGN cohorts in the UK, both native and post-transplant. • Pegcetacoplan is well tolerated in the clinical trial cohort with clear mitigation strategies with respect to risk of infection due to encapsulated organisms and meningococci

Thank you for your time.

Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	National Renal Complement Therapeutics Centre, Newcastle University/ The Newcastle upon Tyne Hospitals NHS foundation trust. National Renal Complement Therapeutics Centre
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The National Renal Complement Therapeutics Centre is a collaboration between Newcastle Upon Tyne Hospitals NHS Foundation Trust and Newcastle University and was commissioned by NHS England to provide the National aHUS and C3 Glomerulopathy highly specialised services. It is funded by NHS England and NHS Scotland.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Funding for work carried out by Professor David Kavanagh Alexion/ Astra Zenica Research Grant £ 179,777.50 Conference travel Sobi £4,347.58 Advisory boards Novartis. £5,466.88 Steering committee member FDA Advisory Committee nominee & advisor EU rapporteur Advisory boards/Lectures
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Ultimately the aim of treatment with C3G /IC-MPGN is to stop end stage kidney failure, however, it is not feasible to evaluate this in clinical trials as progression to end stage kidney failure occurs over a 10-15 year period in ~50%. This problem with clinical endpoints was specifically addressed by the Kidney Health Initiative (KHI), a public–private partnership between the American Society of Nephrology and the US Food and Drug Administration (FDA). For a more detailed summary- Clin J Am Soc Nephrol. 2024 Sep 1;19(9):1201-1208). This expert panel assessed the currently available data supporting the efficacy end points (1) proteinuria, (2) eGFR, and (3) histopathology. In essence, in a disease where the pathophysiology of disease is exquisitely known (i.e. activation of the alternative pathway {AP} of complement), blockade of the AP associated with a favourable effect with lowering of proteinuria, stabilization, in eGFR and improved histologic changes provides convincing evidence of efficacy, They specifically noted that complete alignment of all 3 end points would not be required.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The KHI reviewed the evidence for treatment thresholds and concluded that there was a lack information on the minimum thresholds for change in any of the three end points (1) proteinuria, (2) eGFR, and (3) histopathology that would be considered clinically meaningful in C3G/IC-MPGN. With regards to the primary endpoint of the trial- a significant reduction in proteinuria- it is known from natural history studies that decrease in proteinuria between 0-12 months was associated with lower kidney failure risk.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There is currently no treatment with good evidence for efficacy in C3G/IC-MPGN. Patients progress to end stage kidney failure despite standard of care. The disease recurs after kidney transplantation and there is no treatment currently that prevents this.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Current standard of care would rely on supportive treatments (e.g., blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors or AT1-receptor blockers) with or without mycophenolic mofetil (MMF) and corticosteroids. Standard of care is based on these guidelines -Kidney Disease: Improving Global Outcomes Glomerular Diseases Work G. KDIGO 2021 Clinical practice guideline for the management of glomerular diseases. <i>Kidney Int</i> 2021; 100: S1–S276. 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. Blockade of the renin-angiotensin-aldosterone system would be considered routine for most proteinuric renal diseases. MMF and corticosteroids are given however there is general agreement that the evidence for their use is poor-based on retrospective uncontrolled studies. The new technology would replace MMF and corticosteroids . Blockade of the renin-angiotensin-aldosterone system would remain as part of the treatment with pegcetacoplan. There is an NHSE policy for the use of Eculizumab for recurrence after kidney transplantation in very specific circumstances however this acts too late in the complement pathway to be effective. Eculizumab is not a comparator for pegcetacoplan in C3G-IC-MPGN Iptacopan is another alternative pathway complement inhibitor that met its primary end point in a phase 3 randomised controlled study of C3G however this was recently evaluated by NICE and was not recommended on grounds of cost. As such it is not routinely used in the NHS, except on a compassionate used basis.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	KDIGO guidelines
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The care pathway would follow KDIGO guidelines. There is little in the way of differences of opinion in treatment- generally following KDIGO guidelines. It is accepted that the evidence of the current standard or care (MMF & steroids) is very poor.
9c. What impact would the technology have on the current pathway of care?	Pegcetacoplan would replace MMF and corticosteroids. The data available from trials would suggest that this will delay or possibly prevent progression to end stage kidney failure. This would prevent dialysis and the need for renal transplant. The disease relapses in ~80% post renal transplant and the trial data suggests that treatment with Pegcetacoplan would delay failure of the transplant. Iptacopan is another alternative pathway complement inhibitor that met its primary end point in a phase 3 randomised controlled study of C3G however this was recently evaluated by NICE and was not recommended on grounds of cost.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Pegcetacoplan would replace MMF and corticosteroids . The data available from trials would suggest that this will delay or possibly prevent progression to end stage kidney failure. This would prevent dialysis and the need

	for renal transplant. The disease relapses in ~80% post renal transplant and the trial data suggests that treatment with Pegcetacoplan would delay failure of the transplant.
10a. How does healthcare resource use differ between the technology and current care?	Pegcetacoplan is a sub cutaneous injection so will require training for patients. Steroids and MMF (and iptacopan) are all tablets requiring no training We would suggest prophylactic antibiotics, which would not normally be given with standard of care- corticosteroids & MMF. This would be an extra tablet Vaccination would be required; a measurement of vaccination titre; and revaccination as required. This is not currently performed with MMF and corticosteroids .
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This agent should be used in the setting of a highly specialist service.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Key investments will be 1) improved pathology services to ensure correct diagnosis 2) improved complement diagnostics (e.g. C3, C4 & C5 Nephritic factors and complement component Abs) to allow adequate dosing and cessation (e.g. if nephritic factor titre wanes) 3) mechanism to ensure adequately vaccinated against meningococcal disease- although this is an extension of the service already provided for eculizumab /ravulizumab use in aHUS

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The clinical trials of pegcetacoplan in C3G does provide evidence of clinically meaningful benefits compared to current standard of care. The data suggests that pegcetacoplan will delay progression of renal failure (both in native and post-transplant disease) and the need for dialysis.
11a. Do you expect the technology to increase length of life more than current care?	It is an extrapolation to comment on any increase in life expectancy based on short term studies with proteinuria as the primary end point although it is not an unreasonable assumption to make that preventing end stage renal failure will increase length of life.
11b. Do you expect the technology to increase health-related quality of life more than current care?	I would expect improved quality of life on pegcetacoplan vs standard of care based on delaying progression of renal failure.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The pathophysiology of disease is well understood (i.e. activation of the AP of complement) and therefore the therapy (therapeutic blockade of the AP) would be expected to work in all individuals including those with recurrence post renal transplant.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Pegcetacoplan is a sub cutaneous injection so will require training for patients We would suggest prophylactic antibiotics, which would not normally be given with standard of care- corticosteroids & MMF. This would be an extra tablet Vaccination would be required; a measurement of vaccination titre; and revaccination as required. This is not currently performed with MMF and corticosteroids .

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There should be rules for starting and research to determine drug cessation. Starting therapy will be based on initially a renal biopsy. Renal pathology services will need alignment across the UK as currently the gold standard tests to diagnose C3G/IC-MPGN are not available in all. I would suggest a group of 3 renal pathologist in the UK to review any biopsy prior starting treatment. There will be exclusion criteria based around secondary causes of C3G/IC-MPGN(e.g. infection, monoclonal gammopathies etc) NICE should dictate a programme of research to determine when the drug should be stopped prior to end stage kidney failure. Currently there is no data on drug cessation and, given the pathogenesis of disease, long term treatment may be required. As the majority of C3G/IC-MPGN cases are secondary to autoantibodies to complement proteins if the autoantibodies waned over time, it could be predicted that the drug could be stopped. This would require additional autoantibody tests. Although obvious, it is probably worth stating that, if the patient reaches end stage kidney failure, pegcetacoplan should be stopped.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I am not an expert in health economics / QALY calculations and cannot comment on this.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The treatment is innovative The condition is extremely rare The treatment is highly specialised The technology offers substantial benefits likely not captured by standard methodologies The condition has a significant impact on patients
16a. Is the technology a 'step-change' in the management of the condition?	This is a step change in the management of C3G.
16b. Does the use of the technology address any particular unmet need of the patient population?	Until now there was no treatment that was shown to improve outcome for patients with C3G/IC-MPGN. As such there is a large unmet need.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile appears relatively benign from the trial data. There is the potential risk of sepsis from encapsulated microorganisms from complement blockade but this risk is known and manageable with prophylactic antibiotics and vaccination.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The trials contained a large number of UK patients, so the trial is a good representation of UK practice. .

Professional organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes from this trial are 1) The significant improvement in proteinuria. It is known from natural history studies that decrease in proteinuria between 0-12 months was associated with lower kidney failure risk. Kidney International 2025 (https://doi.org/10.1016/j.kint.2025.06.003.) 2) The improvement in eGFR relative to the control arm 3) The improvement in C3 staining on kidney biopsy This speaks of the mode of action of the drug with regards to the disease pathogenesis. 4) The improvement in serum C3 level. This speaks of the mode of action of the drug with regards to the disease pathogenesis. I am not aware of any data linking this marker to long term outlook however it is important as it demonstrates that the drug is doing what we expect i.e blocking the complement activation that causes disease. The normalisation of C3 suggests that we are stopping the cause of disease- especially in the context of reduced proteinuria and eGFR stabilization
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, see above

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any other adverse effects out with the clinical trials and pegcetacoplan is used in PNH currently
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real world data in C3G/IC-MPGN is limited however in the C3G / IC-MPGN patients given compassionate use the response seems at least as good as in the trial. The safety profile in PNH appears similarly benign.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Data currently does not include paediatric under 12 years. I do not think there any other equality issues
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• There is currently no evidence based treatment for C3G or IC-MPGN. • Despite the current non evidence based standard of care most patients progress to end stage renal failure • In 80% of cases the disease recurs in transplanted kidneys resulting in graft loss • Pegcetacoplan, improves proteinuria, eGFR and renal pathology relative to placebo both in the native kidney and renal transplants • Clinically pegcetacoplan (or the iptacopan for C3G) should be used first line for treatment of C3G / IC-MPGN

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Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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2. Name of organisation	NHS England
3. Job title or position	
4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England commissions a highly specialised service for aHUS from the national centre in Newcastle. An objective of this service is to provide advice to clinicians on other complement related renal disorders including C3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN). NHS England has commissioning responsibility for the service specification and policies for aHUS and C3G as retained services as defined within the Manual of Prescribed Specialised Services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national, disease-specific NICE guidelines for primary C3 glomerulopathy (C3G) or primary immune-complex MPGN. Treatment is currently supportive and guided by specialist nephrology practice, local protocols, and existing national commissioned pathways for related complement disorders (for example, aHUS commissioning arrangements). Clinical practice varies regionally, reflecting the ultra-rare nature of these disorders and limited licensed pharmacologic options.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not defined nationally. Many patients are managed within local renal centres; more complex cases and diagnostic confirmation are referred to tertiary/centre services with specialist complement expertise. There is variation in diagnostic approaches, genetic/complement testing availability, and when/where novel complement inhibitors are considered; this leads to regional differences in access and management. Provision of advice is included in the service specification for the national aHUS service but treatment options for this group of patients is limited currently and current management oversight provided in Newcastle is for a subset of C3G patients only. https://www.england.nhs.uk/wp-content/uploads/2017/04/atypical-haemolytic-uraemic-syndrome-all-ages.pdf NHS England also has a published routine commissioning policy on the use of eculizumab in the treatment of recurrence of C3G post kidney transplant and a not routinely commissioned policy on the use of eculizumab in the prevention of recurrence of C3G post kidney transplant https://www.england.nhs.uk/wp-content/uploads/2017/02/clin-comms-policy-16054p.pdf https://www.england.nhs.uk/wp-content/uploads/2018/07/Eculizumab-in-the-prevention-of-recurrence-of-C3-glomerulopathy-post-kidney-transplant.pdf Initial discussions suggest there is broad clinical consensus on the pathway of care required to best manage this group of patients.
8. What impact would the technology have on the current pathway of care?	If approved, pegcetacoplan would require a formalised tertiary referral/diagnostic pathway for C3G and primary IC-MPGN to: confirm diagnosis, stratify patients for treatment, provide initial doses and monitoring, and co-ordinate shared care with local renal services if appropriate. Vaccination and infection-risk counselling pathways (meningococcal, pneumococcal, Hib, plus post-vaccination monitoring and antibiotic prophylaxis where appropriate) will need clear protocols. Overall, commissioning would need to create an agreed referral and shared-care model so prescribing, monitoring and adverse-event management are safely delivered. If iptacoplan for treating complement 3 glomerulopathy [ID6283] is recommended by NICE it can be expected that work to develop commissioning pathways relevant to pegcetacoplan would be completed as part of implementation.

Commissioning organisation submission

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Pegcetacoplan is not yet used in NHS practice for C3G / IC-MPGN (it has been used in other indications such as Paroxysmal Nocturnal Haemoglobinuria (PNH)). The current highly specialised service pathway manages a small subset of C3G patients, the wider cohort of C3G/IC-MPGN patients is managed in local renal centres.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Pegcetacoplan represents a novel proximal complement inhibitor (C3 level) and would be a new targeted therapy rather than standard supportive care. Delivery (subcutaneous self-administration or clinic administration) and monitoring differ from current standard practice; clinicians will need to follow specific dosing and safety instructions and adopt vaccination/infection mitigation measures.
10a. How does healthcare resource use differ between the technology and current care?	Noting the comment on ID6283. A commissioned diagnostic and management pathway will be required to facilitate patient access to the new treatment if approved. It is anticipated this will require additional healthcare resource. Increased tertiary input: new/expanded role for specialist centres for patient selection, initiation and monitoring. Drug delivery resources: initial training for subcutaneous administration and ongoing dispensing (clinic vs home delivery). Vaccination and infection prevention: pre-treatment vaccination and possibly short-term antibiotic cover if treatment urgent prior to completed vaccinations. Monitoring: regular renal function tests, proteinuria measurement, and safety monitoring for infections and other adverse events.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Anticipated tertiary pathway for diagnosis and management advice with shared care with secondary renal services is likely to be the main route for prescribing and monitoring. The clinical model would need further discussion and agreement within NHS England. Home administration may be appropriate for stable patients following training.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Not quantified, the expectation is that a diagnostic and management pathway will need to be established for C3G/IC-MPGN (complement testing, histopathology review) with national oversight. The clinical model will need further discussion and agreement within NHS England. Staff training on drug administration (subcutaneous technique), adverse-event recognition, and infection risk mitigation. Patient education materials and mechanisms for home delivery / clinic infusion capacity where required. Commissioned vaccination and prophylaxis protocols and potentially access to rapid response pathways for suspected invasive infection.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Not in current use
11. What is the outcome of any evaluations or audits of the use of the technology?	Not evaluated, not in use currently

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	The disease affects people of all ages, starting in childhood and young adulthood, men and women are equally affected. The requirement for specialist diagnostics and repeated clinic visits could disadvantage those with limited mobility, transport or socioeconomic challenges. If recommended consideration will need to be given to supporting actions to mitigate inequalities.
12b. Consider whether these issues are different from issues with current care and why.	The equality issues are broadly similar to current highly specialised therapies for rare renal disease but could be amplified by the need for specialist initiation and enhanced monitoring. Home administration options and clear shared-care agreements can mitigate some of these access inequalities.

Thank you for your time.

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Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Monday 22 December 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Part 1: Treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Sally Johnson
2. Name of organisation	National Renal Complement Therapeutics Centre and Great North Children's Hospital, Member of BAPN
3. Job title or position	Consultant Paediatric Nephrologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians. ☒ A specialist in the treatment of people with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? ☒ A specialist in the clinical evidence base for primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

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(If you tick this box, the rest of this form will be deleted after submission)	(NB I wrote the BAPN submission and my responses to Q's 1-15 are drawn from that response with some additional points, Q's 16 onwards are additional responses)
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To reverse acute disease To stop progression of disease To prevent end-stage kidney disease
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in proteinuria by at least 50% Reduction in urine protein creatinine ratio to < 100mg/mmol (not possible in all cases) Stabilisation or improvement of eGFR slope References - Masoud et al Kidney International 2025 - Caravaca-Fontan et al Kidney International Reports 2025 - Nester et al Clin J Am Soc Nephrol 2024
10. In your view, is there an unmet need for patients and healthcare professionals in primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis?	There is definitely an unmet need for patients with C3G and IC-MPGN, which leads to an unmet need for healthcare professionals. This is because existing treatments do not address the underlying cause of the disease, have limited efficacy and have significant and debilitating side-effects (such as high dose corticosteroids).
11. How is primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	I will limit my comments throughout this response to the treatment of children and young people (CYP) aged 12-18 years. Current treatment:

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• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	• CYP with IC-MPGN and C3G are treated with a range of agents, depending upon severity of disease. • CYP with relatively mild disease (e.g. normal kidney function, low level proteinuria) are generally treated with either ACE inhibitors or angiotensin receptor blockers to provide RAAS inhibition (RAASi). • CYP with moderate disease (e.g. moderate proteinuria, mild impairment of kidney function) are treated with high-dose oral corticosteroids and oral mycophenolate mofetil (MMF) in addition to RAASi. If there is a response (e.g. reduction in proteinuria) then corticosteroid dose is generally weaned to low-dose or stopped and MMF is continued, often for 2 years or more, before attempting to wean off. If there is lack of response then immunosuppression is weaned off after several months. In case of lack of response to immunosuppression, CYP are managed by maximising RAASi, using diuretics for oedema and anticipation of the complications of a nephrotic state e.g. thrombosis, infection. • CYP with severe disease (e.g. grossly nephrotic state, declining kidney function) are generally managed as an in-patient with IV corticosteroid, followed by oral steroids, a trial of MMF and/or escalation to more powerful immunosuppressive agents such as cyclophosphamide or rituximab. In some cases, regular plasma exchange is attempted as treatment options are exhausted and kidney failure appears inevitable. • Children with severe IC-MPGN and C3G will require kidney replacement therapy (ie dialysis) both acutely and/or long-term when end-stage kidney disease develops (ESKD). Kidney transplantation can be performed, although there is a high risk of recurrence and graft loss (Obata Transpl Rev 2024). • CYP may fluctuate between severity groups over time such that treatment may need escalating and weaning repeatedly during the disease course.

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	Clinical guidelines: • The main guideline currently used in the UK is the KDIGO (Kidney Disease – Improving Global Outcomes) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases – Chapter 8 “Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury” • The management of CYP with C3G and IC-MPGN has recently been included in the “Clinical practice recommendations for the initial immunosuppressive treatment for children and young people with immune mediated glomerular diseases – a British Association of Paediatric Nephrology/UK Kidney Association harmonisation project”. This is recently published on the UK Kidney Association website FINAL VERSION Treatment of immune mediated glomerular diseases in children guideline 291025_1.pdf. Current pathways of care: • Up until now, the general approach to the management of CYP with C3G and IC-MPGN has been broadly similar across the UK but there has likely been unwarranted variation in terms of dosing and length of corticosteroids and escalation of therapy beyond corticosteroids and MMF. • The National Renal Complement Therapeutics Centre in Newcastle provides ad hoc advice to clinicians managing patients with IC-MPGN and C3G in England and Scotland (funded) and to Wales and N Ireland (unfunded). Impact on pathways:

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	• The results from the VALIANT trial are highly encouraging, indicating a dramatic reduction in proteinuria in CYP with C3G and IC-MPGN with pegcetacoplan. In addition the biopsy data showing disappearance of C3 from the kidney biopsy (albeit in adult participants) suggest that the root cause of the kidney disease is being targeted. • Although the clinical trial did not address the optimal timing of pegcetacoplan treatment within the care pathway, I think that it is likely that CYP who receive pegcetacoplan early in their disease course would need less (if any) conventional immunosuppression. I think it is also likely that fewer CYP with C3G/IC-MPGN will require treatment with dialysis following treatment with pegcetacoplan.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Most current therapy is administered as oral medication. Pegcetacoplan is administered by twice weekly sub-cutaneous infusion. Use of the technology should be led by tertiary care in CYP, in some cases with a shared care arrangement with secondary care (a general paediatrician with a specialist interest in nephrology). There may be benefit of having oversight from a national service to ensure uniformity of access to diagnostic testing and to expedite learning regarding the place of pegcetacoplan in long-term treatment (e.g. understanding who can withdraw from therapy and who needs to continue) analogous to the use of C5 inhibition in atypical HUS. The role of specialist renal histopathologists (and associated technical laboratory support) in the diagnosis of C3G and IC-MPGN is absolutely crucial. Distinguishing between C3G/IC-MPGN and other rare glomerular disorders can be challenging and sometimes requires a second histopathology opinion. In cases where there is diagnostic doubt, use of generic immunosuppression has been a reasonable approach. However now that there is a targeted treatment,

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	the differential diagnosis becomes even more crucial (e.g. exclusion of acute post-infectious GN or paraprotein mediated disease or lupus). I think that investment into renal histopathology (for example in a special interest network for discussing cases) may be needed to help to direct appropriate use of pegcetacoplan. There will also need to be adequate safety oversight e.g vaccination status, monitoring of infection risk.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	Absolutely – yes. Treatment for C3G/IC-MPGN should be aiming for minimal residual proteinuria. Although partial remission of disease achieved by conventional immunosuppression (e.g. significant reduction in proteinuria) has been welcomed, the long term consequences of any residual proteinuria in CYP will have long term impact in terms of kidney survival over a lifetime. We do not have head-to-head data of conventional treatment vs pegcetacoplan, however many of the patients in the VALIANT trial were already on conventional therapy and still met the entry criteria. The trial data suggests impressive reduction in proteinuria. The current immunosuppressive treatments used in children have variable efficacy and significant toxicity. High dose corticosteroids have well-documented negative effects such as hypertension, hyperglycaemia, loss of bone mineral density. However in CYP, the impact on growth and achievement of final adult height, neurocognitive/neuropsychiatric effects and cosmetic effects such as acne and obesity contribute to limited adherence and impaired quality of life. Thus, I think that pegcetacoplan will have better efficacy and reduced toxicity compared with current care.

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	CYP with ESKD have reduced life expectancy. The expected number of life years lost in children with kidney failure ranges from 16 to 32 years (Wyld JASN 2023) – therefore I expect the technology to increase length of life more than current care. The quality of life of adolescents starting dialysis (in terms of leisure activities, physical well-being, relationships with friends and energy-vitality score) is lower than in healthy adolescents (Clave BMC Nephrology 2019) – therefore I expect the technology to increase quality of life more than current care. I anticipate fewer CYP would need to commence dialysis if receiving pegcetaplan.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In terms of CYP, I don't think so.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There are pros and cons of this comparison Subcutaneous use of pegcetacoplan will require training and ongoing supervision, most likely by specialist nurses. There may also be implications for pharmacy dispensing and disposal of used devices. Some CYP may have procedural anxiety and require some clinical psychology support to access the technology. This is generally available within the paediatric nephrology MDT caring for the CYP. However, some CYP struggle to take their oral medications regularly and would benefit from a supervised twice weekly subcutaneous injection.

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16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would imagine that a “treat early, save nephrons, withdraw if possible” approach would be ideally suited to this technology, similar to the approach with C5 inhibition and aHUS. However, C3G and IC-MPGN are often driven by acquired autoantibodies such as nephritic factors. If a positive nephritic factor subsequently tests negative, there would be a rationale for stopping treatment under close supervision. In addition, a minority of patients may undergo spontaneous remission, and therefore a trial of stopping therapy under close supervision could be considered reasonable to see if disease activity has settled during treatment. There is a group (perhaps <10%) who present with an rapidly progressive picture in whom (assuming they have a good response to the technology), an attempt at stopping would seem unwise, at least in the first couple of years. Most patients fall into a middle group with persistent active disease, likely driven by a factor that continues to be present. Whether these patients can successfully stop treatment, or receive episodes of treatment, remains to be determined. Stopping therapy would need close monitoring and the ability to restart quickly once parameters deteriorate.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes ESKD has a massive impact on non-health outcomes. The wider impact of a CYP developing ESKD – e.g. on parental employment and mental health, impact on siblings (mental health) and future employment also should be considered. If pegcetacoplan can stop/delay development of ESKD, these are significant benefits which should be explored. For children, PedQL can be used to capture quality of life data that includes school functioning. Stories from patients and families with lived experience

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	should be included in the outcome assessment to capture these unmeasured potential benefits. Some references are included below: The significance of relationships and dynamics in families with a child with end-stage kidney disease: A qualitative study - PubMed (nih.gov) Experiences of parents who have children with chronic kidney disease: a systematic review of qualitative studies - PubMed (nih.gov)
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes. It is a treatment that targets the underlying cause of the disease. Instead of treating the kidney inflammation that is caused by C3 deposition in the kidneys, it stops C3 deposition in the kidneys – thus it is a step-change. If used early in the disease course, it is likely to change C3G/IC-MPGN from chronic conditions that require intensive follow up and progress to ESKD, to conditions that can be kept quiescent. The focus of management is likely to switch to how long therapy is needed and when it needs to be reinstituted. I consider that the technology is innovative and will make a substantial impact on health related benefits. I anticipate it will effectively treat C3G/IC-MPGN, stop disease progression and development of CKD, and prevent end-stage kidney disease and the need for transplantation in a large proportion of patients. This depends upon timely diagnosis and early treatment - I treat a lot of CYP with minimal chronic damage on their biopsy at the time of diagnosis. It addresses the unmet need that there are no treatments to switch off C3G/IC-MPGN and prevent progression to kidney failure. CYP who have even mild CKD by age 18 years will most likely develop end-stage kidney failure during their lifetime. It also addresses the unmet need for a treatment that does not have the toxicity of prolonged, high-dose corticosteroids, which are particularly debilitating during adolescence (weight gain, acne, mood changes, hypertension and diabetes, impaired growth, non-targetted immunosuppression).

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19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side-effect will be a risk of infection. This will require a patient to be vigilant for signs of infection and seek medical review. In reality, this would happen anyway for adolescent patients under specialist care for these conditions. In addition, this technology is likely to reduce the need for dialysis and transplantation, both of which are associated with significant increased risk of infections. Subcutaneous use of pegcetacoplan will require training and ongoing supervision, most likely by specialist nurses. Some CYP may have procedural anxiety and require some clinical psychology support to access the technology. This is generally available within the paediatric nephrology MDT caring for the CYP.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	On the whole, yes. However these were prevalent patients who had already experienced a number of other therapies. Moving forward, there will be a need to use the technology earlier in the disease course (which applies to all countries). In my view, the key outcomes are reduction in proteinuria and stabilisation or improvement in eGFR. These were both assessed in the trials. These are surrogate markers for a reduction in end-stage kidney disease and there is good data, particularly for proteinuria reduction, that these are good surrogate markers. (References - Masoud et al Kidney International 2025 - Caravaca-Fontan et al Kidney International Reports 2025 - Nester et al Clin J Am Soc Nephrol 2024). C3d deposition was assessed in the trials. It is not known if this adequately predicts long term clinical outcomes. However reduction in C3 deposition is very persuasive that the underlying etiology is being treated

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	I'm not aware of adverse effects not reported in the trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Ortiz Pediatr Nephrol 2025 describes 3 pediatric and adolescent patients with similar outcomes to the trials Guzman Nephrology 2025 describes a pediatric patient with similar response Mancuzo Pediatr Nephrol 2025 describes pegcetacoplan in 5 pediatric patients with similar outcomes to the trials NB these are generally patients younger than the trial cut-off of 12 years and above.
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	The trials only included adolescent patients aged 12 years and above Under 12-year-olds were not included in the trials and the appraisal is only for those aged 12 years and above. Thus, those under 12 years with C3G and IC-MPGN will not have routine access to this technology and children may progress to kidney failure whilst adults may well not. This must be addressed in trials for those under 12 years urgently. Of note, in the UK cohort of CYP with C3G/IC-MPGN published in cJASN (Wong 2021), 63/80 presented before the age of 12 years. Currently, standard immunosuppression is available to all regardless of age.

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• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
Key issue 1 – population 24. Would pegcetacoplan be used to treat people with chronic kidney disease (CKD) stage 4, and those not on dialysis/transplanted with CKD stage 5?	CKD stage 4 – I would say yes – anything that delays onset of ESKD is of value, particularly in those aged under 18 years CKD stage 5/dialysis – I would say no as likely to be too late. NB if someone presented with AKI and an eGFR <15 with active inflammation on biopsy that is different to CKD 5 and they would likely receive treatment
Key issue 2 – comparators 25. Is eculizumab a relevant comparator for this appraisal? 26. If so, what proportion of people aged 12 years and older with primary complement 3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) receive eculizumab in clinical practice?	No it is not. There is insufficient evidence of benefit of eculizumab in C3G/IC-MPGN and it targets the wrong part of the complement pathway for most patients with C3G Very few patients with C3G/IC-MPGN in the UK receive eculizumab in clinical practice
Key issue 3 – treatment waning The model assumes no waning of relative treatment effect, i.e., a constant pegcetacoplan + standard of care (SoC) treatment effect over a patient's lifetime. The company	I have no reason to expect the effect of pegcetacoplan would wane over time, due to its biological mechanism of action.

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said that this was based on the VALIANT trial and the mechanism of C3 inhibition. 27. Please comment on the clinical plausibility of assuming no treatment waning and if there is a scientific rationale to expect the pharmacological effect of pegcetacoplan to wane over time?	
Key issue 4 – baseline C3 level as a potential treatment effect modifier The VALIANT clinical trial subgroup analyses of baseline C3 level (low or normal) showed significant differences in the outcomes of proteinuria and eGFR at week 26 between the subgroup of baseline low C3 level and the subgroup of baseline normal C3 level. The external assessment group (EAG) have noted that this means that baseline C3 level is a potential treatment effect modifier. 28. Would you expect there to be significant differences in the outcomes of proteinuria and estimated Glomerular Filtration Rate (eGFR) at week 26 between the subgroup of baseline low C3 level and the subgroup of baseline normal C3 level? If so, why?	I don't think so. We know that standard assays of C3 in most laboratories don't differentiate intact C3 from its degradation products. Therefore a normal C3 level does not mean that there is not active complement turnover in the plasma. Thus, a low C3 is helpful to indicate complement turnover but a normal C3 does not exclude this. And so I would not use this to determine whether treatment is going to be effective. If the biopsy has C3 deposition ++ then that indicates that complement is being activated
Key issue 7 – inclusion of stable disease health state The company has included a stable disease health state, defined as urinary Protein-to-Creatinine Ratio (uPCR) less than 0.5 g/g. For patients in the stable disease health state, it was assumed to not experience eGFR decline or transition to later CKD stages. 29. Please comment on the existence of a "stable disease" phase (where patients "maintained stable eGFR") in C3G.	29. "Stable disease phase" – in the current landscape, <i>some patients</i> may respond to RAASi or immunosuppression and have a period of low level proteinuria. I would hope this will be a higher proportion with the technology 30. I agree that <i>a proportion</i> of patients can stabilise with regard to their eGFR without progression of CKD (but the proteinuria would need to remain at that very low level). Note however that CYP with persistent low level proteinuria have a risk of falling eGFR over their lifetime.

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30. Please comment on the plausibility that for a proportion of patients their disease can stabilise and that no eGFR decline nor transitions to more severe CKD stages are assumed 31. Please comment on, if applicable, whether stable disease should be defined by uPCR (or different outcome(s)) and whether the cut-off of 0.5 g/g is plausible. 32. Please comment on the plausibility of the assumption that patients who achieve stable disease temporarily discontinue their treatment and continue again when relapsing.	31. Yes I think that stable disease should be defined by uPCR and I think that 0.5g/g is plausible, however patients would need to continue sufficient RAASi to keep this as low as possible. 32. This is very difficult to answer because we have not seen this technology used in that way. I consider that patients will fall into three main groups: i) milder disease who will have a good response to a short period of treatment and can stop without recurrence ii) severe onset (eg, rapidly-progressive GN) in whom one would find it difficult to consider stopping the treatment, thankfully a small proportion and iii) the majority who will have good response to treatment and in whom a trial of stopping could be considered, with close monitoring and re-initiation in case of relapse. However if the driver for disease is still present (e.g nephritic factor) then relapse will be likely. It would be important to decide how many attempts at stopping would be reasonable, e.g 2 or 3 before deciding to cease attempts to discontinue.								
Key issue 11 - identical transition probabilities before and after transplant 33. The model assumes identical transition probabilities, (i.e. rate of disease progression), pre- and post-transplant. Is this assumption clinically plausible?	Kidney transplants have a shorter life than native kidneys due to a complex mix of factors e.g. chronic immune-mediated injury, nephrotoxic medications. This is completely separate to the recurrence of disease, which is additive on top of the background risk. So I think C3G progression would probably be the same, but loss of eGFR will be faster in a transplant.								
Key issue 12 and 13 – health-related quality of life The utility values used within the cost-effectiveness analyses are presented below. 34. Based on your clinical experience, do these values seem reasonable for patients in these health states? <table><tr><th colspan="2">Parameter</th><th>Utility Value</th></tr><tr><td rowspan="2">CKD 1</td><td>Remission</td><td>0.91</td></tr><tr><td>uPCR <1 g/g</td><td>0.91</td></tr></table>	Parameter		Utility Value	CKD 1	Remission	0.91	uPCR <1 g/g	0.91	34 and 35. In stages CKD1-4 I think that uPCR>3g/g would be worse than uPCR 1-3g/g because the nephrotic state is unpleasant. However I don't think it matters how much proteinuria someone has in CKD stage 5, they likely feel ill and are nearing dialysis. I wouldn't say that CKD4 and CKD5 values should be equivalent. Someone with an eGFR of 29 will likely have better QoL than one with eGFR 10. Transplant gives better QoL than both forms of dialysis so these numbers don't seem correct.
Parameter		Utility Value							
CKD 1	Remission	0.91							
	uPCR <1 g/g	0.91							

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	uPCR 1 g/g-3 g/g	0.84
	uPCR >3 g/g	0.84
CKD 2	Remission	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	0.75
	uPCR <1 g/g	0.75
	uPCR 1 g/g-3 g/g	0.69
	uPCR >3 g/g	0.69
CKD 4	Remission	0.58
	uPCR <1 g/g	0.58
	uPCR 1 g/g-3 g/g	0.52
	uPCR >3 g/g	0.52
CKD 5	Remission	0.58
	uPCR <1 g/g	0.58
	uPCR 1 g/g-3 g/g	0.52
	uPCR >3 g/g	0.52
Haemodialysis		0.44
Peritoneal dialysis		0.53
Undergoing transplant		0.44
The company decided to pool HRQoL for CKD stages 1 and 2. 35. Do you agree with the company's approach, taking both into account disease presentation and		

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development as well as the number of measurements available at the different stages?			
Key issue 14 – exclusion of pegcetacoplan administration costs The company stated that pegcetacoplan can be administered by a healthcare professional or administered by the patient or caregiver following proper instructions with a commercially available syringe system infusion pump. 36. Is it plausible to assume that all patients would self-administer pegcetacoplan subcutaneously with the use of a commercially available syringe system? 37. If not, what proportion of patients in UK clinical practice are expected to receive pegcetacoplan self-administered, and what proportion by a healthcare professional? 38. Is self-administration of pegcetacoplan likely to result in higher drug wastage due to missed doses?			36. No. Some will require support e.g learning disability, challenging social circumstances. Parents would need to support younger adolescents and may feel reluctant to administer to their child 37. Difficult to say what proportion but maybe up to 10% would need some support. This is often already available within the paediatric nephrology MDT and I can't comment for adult patients 38. Undoubtedly, HCP supervised dosing would result in fewer missed doses but this is unlikely to be feasible. The same would happen if this were an oral preparation since adherence is rarely 100% across the board
Other questions			
39. Are the modelled patient baseline characteristics (below) generalisable to UK clinical practice and the expected UK C3G and IC-MPGN population for pegcetacoplan?			39. For CYP, I can't comment on the age and weight distribution – they would be younger and lighter. For CKD stages (again commenting only for CYP) this looks reflective of the current prevalent C3G/IC-MPGN population, who have had disease for a number of years and have experienced a number of different treatments. However, moving forward I would anticipate that a higher proportion of a prevalent population would be in CKD 1 or 2 rather than CKD3 if they receive early treatment with the technology. For baseline proteinuria, in the UK CYP cohort described in Wong cJASN 2021, 62.5% had nephrotic range proteinuria at presentation (although there may be bias in recruitment in that milder cases may not have been recruited to the cohort).
	Value	Use in the economic model	
Age (mean)	25.97 years	Mortality risk, general population	

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		age/sex disutility	
Weight (mean)	63.09 kg	SoC basket costs	
Percentage male	43.55%	Mortality risk, general population age/sex disutility	
Baseline distribution of CKD stages	CKD 1	45.97%	
	CKD 2	20.97%	
	CKD 3	29.84%	
	CKD 4	3.23%	
	CKD 5	0.00%	
Baseline distribution of uPCR levels	<1g/g	8.87%	
	1-3 g/g	58.87%	
	>3g/g	32.26%	
SoC treatments in the company submission are based on the 'Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines'. This includes ACEi/ARB, immunosuppressants, systemic corticosteroids, and SGLT2i. Treatment regimens are modelled as components			40. Generally yes, although SGLT2i are not licenced in CYP under 18 years of age.
			41. In Wong cJASN 2021 (UK CYP aged 0-18y cohort), 20% received treatment with RAASi only. The remaining 80% received at least one immunosuppressive

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of the SoC basket, along with the proportion of patients receiving each component. 40. Are the treatments used in the modelled standard of care basket generalisable to UK practice? 41. What proportion of people would you expect to receive each SoC treatment included within the SoC basket? 42. Clinically, should these proportions be assumed fixed over time, or is there evidence that patients switch between treatments as their disease progresses?	agent (corticosteroids alone in 28% and corticosteroids plus another immunosuppressant in the remainder) 42. The proportions receiving each treatment would change over time e.g. starting with RAASi, escalating to immunosuppression with disease activity, weaning/stopping immunosuppression if no effect or if disease controlled. May require further immunosuppression with relapse.
The model assumes that patients return to the baseline distribution of uPCR levels from VALIANT following a transplant. 43. Please comment on the plausibility of this assumption.	At time of transplant, the baseline state is that C3G is not active, and therefore many patients will have minimal proteinuria in the early stages post-transplant. Relapse occurs in up to two-thirds of patients post-transplant and the median time to relapse varies between reports but is in the region of 3-14 months (Sinha Glom Dis 2025, Taroua NDT 2020). Once relapse has occurred I would anticipate the trajectory of proteinuria to be similar to native disease.
In the company submission it is stated that “<i>Technically, transitions between any combination of CKD and uPCR health states are allowed</i>”. 44. Please comment on the clinical plausibility of this statement. More specifically, would backward transitions (e.g., from CKD 3 to CKD 2) or bigger jumps (e.g., from CKD 2 to CKD 4 or from uPCR >3.0 to uPCR <1.5 within one model cycle of 3 months) be considered clinically plausible?	Proteinuria can fluctuate, particularly with intercurrent illnesses. It is conceivable that uPCR in an individual patient may fluctuate between the 3 categories, although most likely between neighbouring categories and less likely between the first and third categories. But it is possible. Regarding CKD stage, it should be noted that switching between CKD stages could happen acutely (eg due to dehydration/infection) and recover. It could also happen if a relapse/flare of disease occurred and then back again if treatment were effective. Strictly speaking these transitions are not really between CKD stages, because these imply chronic states. Rather, these would be episodes of AKI on top of CKD which may or may not be reversible.

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In the company's economic model, it was assumed that less than 2% of patients discontinued pegcetacoplan treatment every three months. Patients who progress to CKD stage 5 or require dialysis are also assumed to discontinue treatment, and patients who achieve stable disease discontinue all treatment. 45. What proportion of people would you expect to discontinue treatment every 3 months? 46. Is a constant discontinuation rate for people discontinuing treatment with pegcetacoplan reflective of what would be expected in clinical practice? 47. Would all patients that progress to CKD stage 5 or require dialysis discontinue pegcetacoplan treatment?	45. It is very difficult to answer this because there is no data to refer to. However, in the early months I do anticipate a few patients will be able to discontinue treatment, who perhaps had a transient complement dysregulation that has self-resolved. Given the trial data, it seems reasonable to assume that many patients will have low level proteinuria and a stable eGFR following treatment with pegcetacoplan. The question is not really whether they can discontinue, it is whether they will need to restart and when. I anticipate that there will be a cohort of patients who fail repeated attempts at discontinuation and would need to remain on treatment. Research will be needed to identify such patients. They are also patients who would benefit from eradication of the driver (eg nephritic factors) in order to discontinue pegcetacoplan. Research is also needed to find a way to eradicate them. 46. I can't answer this definitively because I have no experience of starting or stopping pegcetacoplan in people with C3G/IC-MPGN. But it is likely that the time taken to achieve "stable disease state" will be different in individuals and therefore discontinuation would be spread over time. 47. I agree that these patients would discontinue pegcetacoplan

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

C3G and IC-MPGN have a high risk of ESKD and represent an area of unmet need

The lifelong impact of developing ESKD in early life is immense and hard to quantify

The technology is a targeted treatment that represents a step change in management

Early access to treatment will be key to reduce nephron loss, combined with a programme to understand who can withdraw from therapy

Equity of access to diagnostic testing (including histopathology, identification of disease drivers) should be considered

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Single Technology Appraisal

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In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Part 1: Treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Edwin Wong
2. Name of organisation	National Renal Complement Therapeutics Centre
3. Job title or position	Consultant Nephrologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians. ☒ A specialist in the treatment of people with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? ☒ A specialist in the clinical evidence base for primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

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7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There are key aims of treatment in C3G and IC-MPGN, consistent with many other glomerular diseases. Appropriate timing of biopsy to diagnosis of disease when there is proteinuria and/or decline in kidney function. Early treatment to stop disease activity of C3G and IC-MPGN to minimise development of chronic kidney disease and preserving excellent kidney function. Prevent or reduce progression to kidney failure due to untreated C3G and IC-MPGN and/or development of chronic kidney disease Delay (or prevent) impact of kidney failure to minimise lifetime risk and burden to patients. Prevent or reduce progression to kidney failure due to recurrence of C3G and IC-MPGN following kidney transplant
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Proteinuria is a significant risk factor for kidney failure and reflects active glomerular disease and subsequent chronic irreversible damage. The mechanism for proteinuria reduction reflects the treatment target. It is likely that any sustained reduction in proteinuria reduction can reduce kidney failure risk. Proteinuria reduction as little as 50mg/mmol at 12 months or 20% reduction have been shown to have statistically significant association with risk reduction of kidney failure. Masoud et al KI 2025 10.1016/j.kint.2025.06.003

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	However the greater the percentage reduction in proteinuria or the lower the amount of proteinuria is likely to associate with greater benefit with complete remission of proteinuria being the ultimate target. Targeting the mechanism of disease is likely to be most beneficial and is an option previously unable to the clinician in the management of C3G and IC-MPGN.
10. In your view, is there an unmet need for patients and healthcare professionals in primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis?	Yes. Patients with C3G and immune complex MPGN often progress to kidney failure requiring dialysis or transplants. Up to half of prevalent patients have kidney failure. Those who have transplants will often have disease recurrence with graft loss affecting at least a quarter of patients within 3 years. Masoud et al KI 2025 10.1016/j.kint.2025.06.003. Median time to kidney failure estimated to be in the region of 10 years. The average age of diagnosis is around 20 years old. There are high rates of disease recurrence resulting in graft loss due to disease recurrence. As a result, there is considerable lifetime risk of kidney failure in patients with C3G and IC-MPGN in spite of treatments described in section 11, including [ACEi/ARB/MMF/Pred]. There have been no formally approved treatments up until the approvals of iptacopan and pegcetacoplan by FDA in 2025. Clinical trials address a group of patients with proteinuria and reasonable kidney function [urine P:CR > 100mg/mmol and eGFR>30], however one group who may have even worse prognosis are the group of patients with eGFR<30 have acute inflammatory renal disease, often crescentic who

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	have potential for recovery but were excluded from clinical trials [eGFR<30, rapidly progressive GN]. Additionally, clinical trials have included children aged 12+ but this excludes a significant number of patients who present with C3G or IC-MPGN at an even younger age.
11. How is primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Supportive treatments including inhibition of the renin-angiotensin system with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for management of chronic kidney disease due to C3G and IC-MPGN More recently, some clinicians will add in a sodium glucose co-transporter 2 inhibitors (SGLT2i) for management of chronic kidney disease resulting from either C3G or IC-MPGN. These treatments only target the resultant damage sustained due to complement activation and inflammation within the kidney. In C3G, If significant proteinuria [proteinuria >1g/day] and/or declining kidney function, immunosuppression with mycophenolate mofetil and corticosteroids. Choice of immunosuppression with mycophenolate and steroids is based on observational data only. In recent years, some patients were enrolled into clinical trials of complement inhibitors instead of starting immunosuppression; others were enrolled into clinical trials of complement inhibitors after inadequate responses following immunosuppression. In refractory cases, clinicians sometimes try other immunosuppression, not limited to cyclophosphamide, rituximab, plasma exchange or eculizumab [Wong et al cJASN 10.2215/CJN.00320121]. These

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	treatments [aside from eculizumab] are not listed in most recent KDIGO guidelines. In IC-MPGN, observational data for choice of immunosuppression is not available but clinicians may choose similar treatments empirically as they would for C3G. In post-transplant recurrent C3G, the high proportion of patients that develop recurrence do so despite immunosuppression that has been commenced as part of transplantation standard of care to reduce risk of allograft rejection. These patients are likely to lose their transplant allografts. In a minority of patients with recurrence, this is aggressive [rapid loss of function, crescents on biopsy] and may be considered for eculizumab under the NHSE clinical commissioning policy 16054/P. Long-term outcomes in those patients who have received eculizumab for this indication appears to be poor based on the experience of the national renal complement therapeutics centre. Therefore long-term outcomes for patients transplanted and develop recurrence are poor with graft loss regardless of whether they are eligible to receive eculizumab or not. Eculizumab is not funded in the NHS for patients without kidney transplants. A similar policy is not available for IC-MPGN. In the EAGLE trial, both C3G and IC-MPGN patients were treated with eculizumab but long-term outcomes were not suggestive of overall benefit of eculizumab in these patients. Ruggerenti et al AJKD 10.1053/j.ajkd.2018.12.046 Specific guidelines are listed: however the evidence for these treatments is all observational and retrospective.

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	KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases https://doi.org/10.1016/j.kint.2021.05.015 NHSE Clinical commissioning policy for post-transplant recurrence of C3G. https://www.england.nhs.uk/wp-content/uploads/2017/02/clin-comms-policy-16054p.pdf Referral to secondary care is standard for onset of proteinuria, CKD and AKI that are possible clinical presentations of C3G and IC-MPGN C3G and IC-MPGN are some of a few differentials of kidney disease that may be made following kidney biopsy, a routine test in secondary care. If either C3G or IC-MPGN is diagnosed or suspected following initial biopsy review: Clinicians should consider if there is an underlying cause of complement dysregulation - Specialist complement testing may be undertaken. Clinicians should also consider possible secondary causes of C3G or IC-MPGN. The key difference between the two is based on interpretation of immune staining on biopsy. A biopsy favouring IC-MPGN mandates consideration of a wider range of possible secondary causes than in C3G. Many clinicians will refer to expert centres for second opinions especially where uncertainty about diagnosis has been raised. Variation in practice can include: • Threshold for kidney biopsy – ie not enough proteinuria or perception of too much chronic damage to justify biopsy. Failure to diagnose disease could impact future treatment options or consideration of recurrence risks following transplant.

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- Discussion with expert centres [though for patients with recurrent C3G, the NHSE policy focuses referrals to the National Renal Complement Therapeutics Centre for consideration of eculizumab].
- Access to complement testing [eg nephritic factors, anti-FH antibodies, genetics] to look for abnormalities of the complement system that associate with C3G and IC-MPGN. Finding an abnormality can increase confidence of diagnosis and mechanism of action.
- immunoStaining techniques in renal pathology vary across England which may make it more difficult to make a diagnosis of C3G or IC-MPGN.
- Access to special stains in renal pathology that might reveal key differential diagnosis of C3G eg pronase digest to look for evidence that C3G is due to a paraprotein that requires other treatments,

The availability of an approved treatment such as pegcetacoplan will further expose any variation in clinical practice as clinicians may review prevalent patients who have ongoing clinically significant proteinuria and ongoing risk of kidney failure and carefully assess incident patients who may have a diagnosis of C3G or IC-MPGN.

Clinicians may consider access to specialist centres where there is expertise in diagnosing and managing C3G or IC-MPGN to obtain specialist complement testing and pathology review at an expert centre, to increase confidence of a C3G or IC-MPGN diagnosis or conversely, more confidently exclude a diagnosis of C3G or IC-MPGN prior to considering a complement inhibitor.

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12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This is a subcutaneous therapy that is currently being used by some patients within ongoing long-term extension clinical trials and compassionate use in C3G and IC-MPGN. It is already being used in patients with PNH. It would be used alongside supportive treatments such as ACEi/ARB in keeping with entry criteria into clinical trials. Clinicians would then likely choose between pegcetacoplan versus mycophenolate or corticosteroids as next line therapies which would reflect clinical trial entry criteria. The absence of controlled data to support the use of mycophenolate and steroids compared to the available data for pegcetacoplan may influence decision making in favour of an alternative pathway inhibitor. Pegcetacoplan is a subcutaneous infusion whereas supportive care (ACE/ARB) or initial immunosuppression [mycophenolate / steroids] or are oral Treatments that are infrequently used and not a significant comparator include Rituximab, cyclophosphamide and eculizumab. These would be intravenous. Plasma exchange would be more intensive and require a vascular catheter, plasma products and nursing expertise to deliver the treatment. Clinical diagnosis and appropriate testing is imperative to ensure accurate diagnosis. Initial diagnosis or suspected diagnosis will be made in secondary care but expert opinion or testing may be requested in specialist centres. Once decision to start treatment has been made, prescription of pegcetacoplan would be made by secondary care teams in renal medicine. There may be discussion with expert specialist centres to support diagnosis and also to help assess clinical response

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	Clinicians already seek expert opinion to help make a diagnosis of C3G and IC-MPGN. There may be potentially a greater emphasis on seeking expert opinion given rarity of disease and less experience of clinicians with C3G and IC-MPGN and complement inhibition. There is also a requirement for vaccinations to mitigate against risk of infection against encapsulated organisms and meningococci. Consideration should be made to make existing diagnostic tests, clinical expertise more readily available to secondary care in the diagnosis and management of C3G and IC-MPGN. The renal biopsy is the main test that is available in secondary care that is specific to making a diagnosis of C3g or IC-MPGN but as highlighted above there is variation in how biopsies are reviewed across the country. Specialist complement testing and specific clinical expertise in C3G and IC-MPGN will not be routinely available in secondary care. Cost of specialist complement tests available at the National Renal Complement Therapeutics Centre is currently invoiced to referring clinicians. It may be necessary to transport biopsy tissue / slides and blood samples for specialist tests and/or interpretation to expert centres. Most notably complement testing eg nephritic factors, anti-FH antibodies, genetics that are only available at a single site, the National Renal Complement Therapeutics centre. In addition, some of these blood tests require additional processing at referring centres and transport to diagnostic laboratories on dry ice.

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	Should also consider how to maximise risk mitigation against infection and whether or not to monitoring vaccination response and offer prophylactic antibiotics.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	Yes. Targeting the underlying mechanism of disease, reduces impact of disease on kidney function and delays time to kidney failure that associates with morbidity and mortality that are both significantly associated with kidney failure.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with acute highly inflammatory disease were excluded from trials due to the acute nature of disease, often with low eGFR in the acute phase of disease. These may have excellent well-preserved kidneys. It is possible these patients have more to be gained if the treatment works in this cohort. Patients with slow indolent decline in kidney function who have pre-existing irreversible kidney disease by the time of diagnosis. These were also excluded from clinical trials and may not benefit as much as other patients. However, treatment could still delay time to kidney failure so whilst no preventing kidney failure the greater time gained to prepare for kidney failure could still allow patients to get pre-emptive kidney transplants. It is possible other subsets of patients with C3G or IC-MPGN with specific complement abnormalities or unrecognised secondary causes may not benefit as much – robust evaluation of treatment outcomes in the real world will help stratify treatment pathways to account for these subsets.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	Pegcetacoplan is a subcutaneous infusion and requires healthcare staff to administer. It is anticipated that patients can be trained to self-administer.

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current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There is need to consider risks of infection [mandatory vaccination against pneumococci, haemophilus influenzae type b and also meningococci], patient vigilance and consideration of additional prophylactic antibiotics. Monitoring of clinical parameters would be standard as per starting any therapy however measuring effect of pegcetacoplan on the complement system is something to consider and would require additional tests compared to current standard of care including some samples that require transport to specialist labs using dry ice.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Review of clinical parameters and biopsy as a minimum to start treatment and robust exclusion of secondary causes of C3G and IC-MPGN as would have been required in a clinical trial setting to ensure appropriate patients are selected for treatment. Evaluation of the complement system would increase confidence of a complement-mediated process. Treatment would be stopped patient if progressed to kidney failure. Other reasons for stopping may be considered if treatment not thought to be effective eg no impact on progressive kidney failure or failure to regulate the complement system. Collection and review of post-treatment longitudinal data would be valuable in stratifying clinical response that may help justify additional stopping criteria and potentially help redefine starting criteria. In clinical trials, most patients rolled over to open-label extension trials so the impact of stopping is not truly known. A programme of research to explore additional stopping criteria including in patients who initially benefit could help determine optimal treatment duration. For example, robust detection of specific abnormalities that dysregulate complement that if no longer present, may mean complement

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	inhibitory therapies such as pegcetacoplan are no longer required. Otherwise stopping would allow the complement system to dysregulate again and cause worsening disease again.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Patients with nephrotic syndrome might reduce proteinuria sufficiently to have non-nephrotic range proteinuria. This would lead to improvements in symptomology and reduced risk of complications of nephrotic syndrome that include oedema, risk of infection and thromboembolic events.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Pegcetacoplan inhibits the alternative pathway of complement which is part of the underlying disease mechanism in C3G and IC-MPGN. It therefore provides a specific targeted for these patients. It demonstrates statistically significant reduction in proteinuria, in a double-blinded randomised control trial over and above current standard of care. The outcome is preserving kidney function and at worst delaying and at best preventing kidney failure, depending upon the extent of any irreversible damage that has been sustained at the point of starting treatment. Strictly speaking, it is the same step change that iptacoplan makes for C3G which was also undergoing evaluation – but pegcetacoplan due to its inclusion criteria in its pivotal trial does provide a further step change in a broader patient group – notably adolescents and IC-MPGN. Regardless, pegcetacoplan would help address the high burden of kidney failure in patients with C3G which represents a huge unmet need for patients and healthcare professionals.

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	In patients who have already reached kidney failure and require dialysis, the mechanism of action in disease is comparable so treatment following transplant will likely reduce the impact of C3G or IC-MPGN on the renal allograft. The effect of pegcetacoplan has been studied in post-transplant patients in clinical trials though numbers are small compared to the number of patients included in trial who have not had a transplant.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Based on the safety data reported in the phase 2 and phase 3 clinical trials of pegcetacoplan in C3G and IC-MPGN, pegcetacoplan appears to be well-tolerated. Due to the mechanism of action of pegcetacoplan, there is likely to be a higher risk of infection due to encapsulated organisms and meningococci. As part of the clinical trials, there is a vaccinations schedule to help mitigate risk of infection. In the clinical trials, only a small number of patients have had infections due to encapsulated organisms and were treated with antibiotics. This is a sub-cutaneous injection which may cause local skin reactions. Having regular sub-cutaneous infections may have an impact on quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes in so far as there is a prevalent cohort of patients with C3G and IC-MPGN in the UK who have ongoing proteinuria [typically urine P:CR >100mg/mol] and eGFR >30/min. These are the patients who were selected for clinical trials of complement inhibition in UK. Patients who have less proteinuria are likely to be at lower risk of kidney failure and did not meet a specified threshold for entry into a clinical trial. This does not equate to an absence of benefit in this patient group. Patients with eGFR <30 fall into two categories – those who have significant chronic kidney disease in whom we wouldn't routinely offer immunosuppression currently and who were not included in trials. The

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	group of patients with eGFR<30 have acute inflammatory renal disease, often crescentic who have potential for recovery but were not eligible for clinical trials. There would be an ongoing unmet need in this group. Trials of pegcetacoplan also include patients who have been transplanted with clinical evidence of recurrence and would also reflect UK practice. A minority of patients with rapid decline in graft function would have been excluded from trials but were subject to the eculizumab policy instead. For post-transplant recurrence, there are patients in UK with under the proteinuria threshold for entry into clinical trials who should also be considered high risk patients. Consideration should be given to treatment of these patients also. Patients with post-transplant recurrence generally could also prevent the more aggressive forms of C3G that currently are eligible for eculizumab as per the policy 16054/P. Proteinuria reduction, stabilisation of eGFR demonstrate clinical impact. Improvements in serum C3, reduction in C3 staining on biopsy and reductions in disease activity on biopsy help infer mechanism of action. All were measured in the trial. Proteinuria reduction is being shown to associate with stabilisation of eGFR and lower rates of kidney failure. Reduction in proteinuria of 30% at 6 months associates with slower eGFR decline and lower rates of kidney failure

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	Caravaca-Fontan et al KI reports 2025. https://doi.org/10.1016/j.ekir.2025.01.024 Reduction in proteinuria of 20% associated with lower kidney failure risk Masoud et al KI 2025 10.1016/j.kint.2025.06.003. I am not aware any new adverse events not specifically reported in the clinical trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real-world experience largely reflects compassionate use. There are limited reports including in younger patients as reported in 5 patients in Mancuso et al DOI: 10.1007/s00467-025-06673-w These patients had similar outcomes to the ones reported in the phase 3 trial and suggest that the treatment was well tolerated. There is compassionate use of pegcetacoplan in England but this experience is unpublished.
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Any potential issues would be related to access to healthcare and therefore inability to make the correct diagnosis. Women of child-bearing ages required specific consent relating to birth control and pregnancy was an exclusion in the clinical trials. Patients under 12 years of age would have been excluded from trials but biologically it is the same disease. There would be a difference in management based on age as a result of this where patients under 12 continue to be treated using a previous historical standard of care.

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belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
Key issue 1 – population 24. Would pegcetacoplan be used to treat people with chronic kidney disease (CKD) stage 4, and those not on dialysis/transplanted with CKD stage 5?	The clinical trial criteria excluded patients with eGFR<30ml/min. For patients with chronic progressive disease, this is CKD stage 4 or 5 and likely to be in the setting of significant chronic damage as evidenced by other exclusion criteria notably glomerulosclerosis >50% and/or interstitial fibrosis and tubular atrophy >50% on biopsy. The benefit of pegcetacoplan won't diminish immediately that a patient reaches CKD stage 4. It is possible that in this group of patients the clinician may consider treatment with pegcetacoplan especially if there is significant active disease as evidenced by inflammatory lesions / proteinuria / rapidly falling eGFR. However benefit in this group would translate into delaying time to kidney failure that in practical terms might allow a patient to come to terms with the severity of their kidney disease or potentially allow more

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	time to prepare for a renal replacement therapy and even a pre-emptive transplant. At a lower eGFR, these benefits far diminish and by CKD stage 5 even in patients on dialysis it is highly unlikely that a clinician would start treatment. In contrast there are patients presenting with low eGFR [$<30\text{ml/min}$] that have very acute inflammatory lesions. These patients have very poor outcomes and current treatments are ineffective. It is likely that clinicians may want to try complement inhibition with pegcetacoplan in these patients as the disease is potentially treatable but do date no treatments have been available and these patients would have been excluded due to the acute nature of disease rather than implausibility of clinical response.
Key issue 2 – comparators 25. Is eculizumab a relevant comparator for this appraisal? 26. If so, what proportion of people aged 12 years and older with primary complement 3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) receive eculizumab in clinical practice?	Largely no given the very low numbers of patients that receive eculizumab for this indication in England. Eculizumab that targets the terminal complement pathway and is generally not considered the correct choice of complement inhibitor in C3G or IC-MPGN. Published data is limited to small case series and its inclusion in KDIGO guidelines is based on expert opinion. In England, In terms of the NHS Clinical Commissioning Policy 16054/P, eculizumab is funded for certain patients with recurrent C3G following renal transplant who have significant decline in function and with crescents. This is a severe phenotype that is uncommon – the policy is overseen by the National Renal Complement Therapeutics Centre and approximately 1 person per year has been treated since the introduction of the policy in 2017. It is possible that some patients have been offered this treatment for native C3G or IC-MPGN but these would have been trust funded and numbers would be extremely low assuming there are any cases currently.

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Key issue 3 – treatment waning The model assumes no waning of relative treatment effect, i.e., a constant pegcetacoplan + standard of care (SoC) treatment effect over a patient's lifetime. The company said that this was based on the VALIANT trial and the mechanism of C3 inhibition. 27. Please comment on the clinical plausibility of assuming no treatment waning and if there is a scientific rationale to expect the pharmacological effect of pegcetacoplan to wane over time?	The affinity of pegcetacoplan and C3/C3b is unlikely to change over time and in terms of mechanism of action the treatment effect is unlikely to wane. That said, progression of disease might occur if the complement system is and has always been incompletely blocked, if disease activity has persisted, even at a low level or if there has been sufficient chronic damage to kidney tissue that worsening of kidney function occurs due to proteinuria associated with irreversible kidney damage.
Key issue 4 – baseline C3 level as a potential treatment effect modifier The VALIANT clinical trial subgroup analyses of baseline C3 level (low or normal) showed significant differences in the outcomes of proteinuria and eGFR at week 26 between the subgroup of baseline low C3 level and the subgroup of baseline normal C3 level. The external assessment group (EAG) have noted that this means that baseline C3 level is a potential treatment effect modifier. 28. Would you expect there to be significant differences in the outcomes of proteinuria and estimated Glomerular Filtration Rate (eGFR) at week 26 between the subgroup of baseline low C3 level and the subgroup of baseline normal C3 level? If so, why?	It is possible that differences within a C3G and IC-MPGN cohort could lead to differing responses in response to a complement inhibitor. Low C3 is considered evidence of consumption of C3 and is the rationale for targeting the alternative pathway of complement in this disease. It is plausible that a patient with lower C3 levels compared to those with normal C3 have a disease activity resulting in greater proteinuria and more rapid decline in eGFR that would therefore result in greater proteinuria reduction and change in eGFR at 26 weeks treatment. Indeed, it is possible that there is a spectrum of complement dysregulation resulting in a wide range of C3: in patients with low C3 this could range from massively depleted to minimally depleted and ultimately to patients with normal C3. Additionally, studies were not powered and randomised to look at small individual sub-groups so any differences described should be considered as part of the overall risk-benefit profile for an individual patient.
Key issue 7 – inclusion of stable disease health state The company has included a stable disease health state, defined as urinary Protein-to-Creatinine Ratio (uPCR) less than 0.5 g/g. For patients in the stable disease health	The goal of treatment in C3G and IC-MPGN, as is the goal in any glomerular disease is to reduce the risk of progression of kidney disease. In complete remission where there is expected to be no proteinuria, then

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state, it was assumed to not experience eGFR decline or transition to later CKD stages. 29. Please comment on the existence of a “stable disease” phase (where patients “maintained stable eGFR”) in C3G. 30. Please comment on the plausibility that for a proportion of patients their disease can stabilise and that no eGFR decline nor transitions to more severe CKD stages are assumed 31. Please comment on, if applicable, whether stable disease should be defined by uPCR (or different outcome(s)) and whether the cut-off of 0.5 g/g is plausible. 32. Please comment on the plausibility of the assumption that patients who achieve stable disease temporarily discontinue their treatment and continue again when relapsing.	risk of progression of kidney disease should be back to healthy baseline where the risk of eGFR decline should be minimal. Therefore reduction of proteinuria to the lowest possible level, potentially be using treatments across multiple pathways should be the goal in C3G or IC-MPGN. At the lowest levels of proteinuria, especially with completely normal eGFR, then transition to more severe CKD stages should be minimal and it is plausible that over a lifetime, that the risk of progression to kidney failure can be minimised. However with existing irreversible loss of nephron that occurs prior to diagnosis and following diagnosis there is sub-optimal control of the underlying kidney disease, patients can be expected to progress though the rate of disease progression [eGFR slope] over a long period of time could be anticipated to correlate with proteinuria. The cut off for proteinuria should be as low as possible for a given patient. A patient with new onset disease with little or no long term damage could be expected to be able to get to minimal proteinuria by targeting the key mechanism for disease activity using a complement inhibitor whereas a patient who has more chronic damage may not be able to reach the lowest levels of proteinuria by switching off disease activity with complement inhibitor and that in addition to complement inhibitor therapy should also receive other anti-proteinuric therapies such as ACEi/ARB/SGLT2i. That said, a target of 0.5g/g is one that we have not been able to achieve in C3G and is a useful minimal aspiration.

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	If a patient reaches a low level of proteinuria, then clinicians will look to reducing or stopping treatments to minimise risk of harm to patients. This is the goal in any disease. It is plausible that individual clinicians may stop pegcetacoplan and assess though it is also reasonable to expect that the abnormalities leading complement dysregulation may still exist and that the complement system then becomes overactive again leading to disease activity. At that point treatment should be continued again though the exact rate of disease relapse in this scenario is difficult to predict without carefully collected data. I would anticipate that this relapse rate could be quite high.
Key issue 11 - identical transition probabilities before and after transplant 33. The model assumes identical transition probabilities, (i.e. rate of disease progression), pre- and post-transplant. Is this assumption clinically plausible?	Post-transplant recurrence is predictable and can be pre-empted by surveillance following transplant. https://pubmed.ncbi.nlm.nih.gov/39116277/ confirms a high rate of histological recurrence https://link.springer.com/article/10.1007/s00467-024-06476-5 significantly lower graft outcomes compared to controls due to C3G recurrence. Post-transplant recurrence of C3G or IC-MPGN should be considered at least as likely to result in graft loss as pre-transplant disease and progression to kidney failure. However due to monitoring, of transplant grafts following transplant there is early detection that allows treatment of recurrence before irreversible damage can occur.
Key issue 12 and 13 – health-related quality of life The utility values used within the cost-effectiveness analyses are presented below. 34. Based on your clinical experience, do these values seem reasonable for patients in these health states?	CKD Stages 1 and 2 are very mild and not normally referred to renal services in UK in isolation. Pooling these two groups with this in mind seems reasonable. More important would be the impact of disease activity due to complement activation in C3G and also proteinuria in particular

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Parameter		Utility Value
CKD 1	Remission	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	0.91
	uPCR <1 g/g	0.91
	uPCR 1 g/g-3 g/g	0.84
	uPCR >3 g/g	0.84
CKD 3	Remission	0.75
	uPCR <1 g/g	0.75
	uPCR 1 g/g-3 g/g	0.69
	uPCR >3 g/g	0.69
CKD 4	Remission	0.58
	uPCR <1 g/g	0.58
	uPCR 1 g/g-3 g/g	0.52
	uPCR >3 g/g	0.52
CKD 5	Remission	0.58
	uPCR <1 g/g	0.58
	uPCR 1 g/g-3 g/g	0.52
	uPCR >3 g/g	0.52
Haemodialysis		0.44
Peritoneal dialysis		0.53
Undergoing transplant		0.44

significant nephrotic syndrome. It is possible that uPCR has a greater negative impact on health than indicated here.

Undoubtedly patients with more severe CKD stages will have worse health states though we might expect a difference between stage 4 and stage 5. In stage 4 CKD some patients might have very few additional complications of CKD [eg anaemia, fluid retention, need for dietary restriction etc] whereas others close to CKD5 might have a full range of complications. On balance, should utility even in CKD stage 3 and 4 be close to normal than CKD stage 5
<https://pmc.ncbi.nlm.nih.gov/articles/PMC7507735/> Health states for patients receiving dialysis will be the lowest.

Lowest utility covers the period of time around the kidney transplant surgery, a major operation. This seems reasonable though this period of time is relatively short in the overall lifetime of patients and where a transplant is successful patients then revert to a health state comparable to non-transplant patients depending on CKD stage and urine PCR. Having said that, any measures to prevent kidney failure in the first instance are preferable to assuming that patients will do better following a transplant.

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The company decided to pool HRQoL for CKD stages 1 and 2. 35. Do you agree with the company's approach, taking both into account disease presentation and development as well as the number of measurements available at the different stages?	
Key issue 14 – exclusion of pegcetacoplan administration costs The company stated that pegcetacoplan can be administered by a healthcare professional or administered by the patient or caregiver following proper instructions with a commercially available syringe system infusion pump. 36. Is it plausible to assume that all patients would self-administer pegcetacoplan subcutaneously with the use of a commercially available syringe system? 37. If not, what proportion of patients in UK clinical practice are expected to receive pegcetacoplan self-administered, and what proportion by a healthcare professional? 38. Is self-administration of pegcetacoplan likely to result in higher drug wastage due to missed doses?	There is potential for all patients to self-administer but some may require parental or other caregiver support. It is plausible that some patients may specifically require support from a healthcare professional and that this need should be anticipated though exact numbers not known. It is possible that self-administration could lead to drug wastage though I would hope that possibility would be low.
Other questions	
39. Are the modelled patient baseline characteristics (below) generalisable to UK clinical practice and the expected UK C3G and IC-MPGN population for pegcetacoplan?	These baseline characteristics seems to reflect characteristics as summarised in 10.1016/j.kint.2025.06.003. These characteristics don't list transplanted patients per se though they may be accounted for purely by eGFR and proteinuria.

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		Value	Use in the economic model
Age (mean)		25.97 years	Mortality risk, general population age/sex disutility
Weight (mean)		63.09 kg	SoC basket costs
Percentage male		43.55%	Mortality risk, general population age/sex disutility
Baseline distribution of CKD stages	CKD 1	45.97%	Starting health state distribution
	CKD 2	20.97%	
	CKD 3	29.84%	
	CKD 4	3.23%	
	CKD 5	0.00%	
Baseline distribution	<1g/g	8.87%	
	1-3 g/g	58.87%	

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of uPCR levels	>3g/g	32.26%		
SoC treatments in the company submission are based on the 'Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines'. This includes ACEi/ARB, immunosuppressants, systemic corticosteroids, and SGLT2i. Treatment regimens are modelled as components of the SoC basket, along with the proportion of patients receiving each component. 40. Are the treatments used in the modelled standard of care basket generalisable to UK practice? 41. What proportion of people would you expect to receive each SoC treatment included within the SoC basket? 42. Clinically, should these proportions be assumed fixed over time, or is there evidence that patients switch between treatments as their disease progresses?				The SOC treatments cited are generalisable to UK practice. For prevalent patients, they may be treated with some or all of the above SOC treatments. The vast majority can be expected to be receiving ACEi/ARB. The usage of MMF / steroids and SGLT2 will differ depending on clinical experience of these treatments in C3G and IC-MPGN and the perception of the evidence for their use. It is likely that patients are more likely to receive MMF / steroids / SGLT2i amongst a prevalent cohort with years of disease as opposed to a newly diagnosed cohort where a clinician may opt to start pegcetacoplan rather than to cycle through a basket of SOC treatments for which the evidence base is weak. Proportion of MMF/ steroids may lessen if patients were already on them and there has been significant clinical improvement since starting pegcetacoplan. Similarly, if clinicians feel that MMF / steroids do not reduce proteinuria and if disease is progressing then they may be stopped. Addition of SGLT2 inhibitors if there is ongoing proteinuria following treatment. Successful treatment with pegcetacoplan should mean less disease progression though if there is worsening disease, then clinicians would likely continue ACEi/ARB/SGLT2 to continue to mitigate the damage done as part of chronic kidney disease. With this in mind, treatments in kidney disease such as C3G and IC-MPGN should be considered complementary rather than mutually exclusive.
The model assumes that patients return to the baseline distribution of uPCR levels from VALIANT following a transplant. 43. Please comment on the plausibility of this assumption.				Patients should have little or no proteinuria from the transplant graft prior to clinical disease recurrence. However, if considering the current prevalent transplant population then it is plausible that the distribution of proteinuria is comparable to that observed in VALIANT.

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In the company submission it is stated that “<i>Technically, transitions between any combination of CKD and uPCR health states are allowed</i>”. 44. Please comment on the clinical plausibility of this statement. More specifically, would backward transitions (e.g., from CKD 3 to CKD 2) or bigger jumps (e.g., from CKD 2 to CKD 4 or from uPCR >3.0 to uPCR <1.5 within one model cycle of 3 months) be considered clinically plausible?	Improvements in proteinuria can take place in weeks so P:Cr can go from nephrotic to non-nephrotic and less than 100mg/mmol very quickly as evidenced in the 26 weeks in the clinical trial and plausibly within a 3 month cycle. Worsening in proteinuria can also be quick and reflect poor control of disease – if in the setting of pegcetacoplan this could be an indication that the treatment doesn’t work for a specific patient or a frank relapse. eGFR changes reflecting a stage jump eg from 2 to 4 would only occur as part of a specific acute deterioration such as crescentic disease which would be very unusual. eGFR changes reflecting a backward transition is possible and probably reflects resolution of significant inflammation at the onset of treatment.
In the company’s economic model, it was assumed that less than 2% of patients discontinued pegcetacoplan treatment every three months. Patients who progress to CKD stage 5 or require dialysis are also assumed to discontinue treatment, and patients who achieve stable disease discontinue all treatment. 45. What proportion of people would you expect to discontinue treatment every 3 months? 46. Is a constant discontinuation rate for people discontinuing treatment with pegcetacoplan reflective of what would be expected in clinical practice? 47. Would all patients that progress to CKD stage 5 or require dialysis discontinue pegcetacoplan treatment?	The 1.65% figure was based on the clinical trial data. It is likely that patients with C3G / IC-MPGN are highly motivated as they potentially have a lot to benefit from an effective treatment. Stopping due to side effects as measured in the current duration of the clinical trials at a rate of 1.65% seems reasonable in the foreseeable future but the practice in the clinic may differ. In the short duration of trials, very few patients will have deteriorated to kidney failure on the basis that they would have eGFR>30 at time of starting. However, over years, these patients could reach kidney failure [CKD stage 5] and it would be appropriate to discontinue treatment. For a group of patients with stable disease, it is plausible that some clinicians may discontinue and restart if disease manifestations worsen. However as discussed in the earlier question, ‘stable’ disease is likely to reflect reduction in urine P:CR to <0.5mg/mmol and probably lower before any consideration of stopping treatment. There would be an expectation

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	that unless the cause of complement dysregulation has been removed that disease relapse is likely and that treatment would be restarted. Over time however, the steady state for treatment discontinuation is likely to be higher for the reasons above but limited to the specific groups as outlined.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

C3G and IC-MPGN have a high unmet need with high rate of progression to kidney failure despite currently available ‘standard of care’ treatments

Pegcetacoplan demonstrates clinically significant reduction in proteinuria as shown in the phase 3 randomised control trial that is likely to reduce long-term rates of kidney failure in patients with C3G and IC-MPGN and benefit patients who develop recurrence following a kidney transplant. The clinical trial population from available phase 2 and phase 3 data fairly reflects the C3G and IC-MPGN cohorts in the UK, both native and post-transplant

Pegcetacoplan is well tolerated in the clinical trial cohort with clear mitigation strategies with respect to risk of infection due to encapsulated organisms and meningococci

Optimal use of pegcetacoplan and natural history of C3G and IC-MPGN in the era of proximal complement inhibitors is ultimately not known

Thank you for your time.

Clinical expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Your privacy

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Clinical expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis or caring for a patient with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis. The text boxes will expand as you type.

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Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm on Monday 22 December 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Part 1: Living with this condition or caring for a patient with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis

Table 1 About you, primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis, current treatments and equality

1. Your name	Alex Gibbs
2. Are you (please tick all that apply)	☒ A patient with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	MPGN/DD Support Group
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Other patient experiences. Own medical knowledge. ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☒ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? If you are a carer (for someone with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis) please share your experience of caring for them	I was diagnosed at age 4 with primary complement 3 glomerulopathy(C3G). I can't comment too much on my experiences when suffering from the disease. I had multiple treatments over about 18 months before reaching ESRD and starting dialysis. Most of what I can say about that time comes from the accounts of family and reading through my records as an adult. Given the lack of an effective treatment, I know I received plasma exchange, cyclophosphamide, and an array of other drugs to try and slow progression of CKD. I had many procedures which were evidently somewhat traumatising at that age, and I know I didn't enjoy taking all the medicines. And for all that, I still progressed to ESRD and needed dialysis. This came with a whole host of consequences including multiple episodes of peritonitis, surgeries for access modalities, an episode of PRES (posterior reversible encephalopathy syndrome), seizures and hallucinations, and eventually a transplant at age 10. That transplant lasted about 7 years before I suffered rejection at the start of the COVID Pandemic in 2020 at age 17. During those 7 years I was able to attend school as a normal child would. I developed my interests in science and during the same period gradually learnt more

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	about my own condition. I attended conferences, learnt from the experts. Having spent so much time in hospitals, becoming a self-proclaimed expert patient, and wanting to gain a deeper understanding of my condition, I was naturally drawn to medicine as I progressed through school. I was luckier than many patients. Though I did get ill again at 17, timings worked out in such a way that I was able to get a spot in medical school, which I now attend. I spent 5 more years on dialysis from 2020, which brought new consequences. More surgeries for access, a nephrectomy, 2 cases of sepsis, a cardiac arrest, pulmonary emboli, and parathyroidectomy before eventually having a second transplant in February 2025. The way I experience C3G has changed throughout my life. I suffered from the disease itself and the attempts to treat it in the early days after diagnosis. But as I have grown up, I experience it more intellectually than physiologically. As I lost my transplant, I was wanting to know whether I had C3G recurrence or not. Having had rejection and getting back to dialysis, I actually felt free from the threat of the disease. But then it became a big consideration again with the second transplant. I would ask the doctors what the plan would be if there was recurrence. The answers were essentially the same as they were all those years ago. They didn't have a good plan. I weighed up the options on my own. I had followed the trials and development of emerging treatments including pegcetacoplan. I have heard from other patients who had been in the trials. And I knew that I couldn't continue my medical studies on dialysis forever. I concluded that there was enough hope for a treatment that I should go ahead with a transplant if the opportunity presented itself. But it still feels like a gamble even now. As I write this I am less than a year post op. At the time of

Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

	the meeting I will still be a few days short of a year. I know chances are higher for recurrence the earlier you are after the transplant. C3G now feels like a shadow over my life. I expect that I will have to deal with it again someday, I just don't know when. I figure my best options are to learn as much as I can and get involved in this sort of opportunity to have some input on new treatments. I want to give myself any advantage possible in case that day does come that I suffer from this disease again. In some ways C3G guided my life. My experiences as a patient have definitely led me to where I am now. In some odd ways I am grateful. But it has also taken so much from me. 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. That stuck with me and still holds true every day.
7a. What do you think of the current treatments and care available for primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a I think current treatments are inadequate. They are not targeted. Treatment recommendations are to control hypertension, lipids and follow a healthy diet. All great, and all good for kidneys, but we know how C3G works. We know that there is complement dysregulation. These treatments don't target complement at all. There seems to be consensus now in recommending prednisolone and mycophenolate mofetil. But again these are not targeted at complement, and based on patient experiences I am aware of, have varying and usually limited levels of success.

Patient expert statement

	After this, some patients have similar experiences to me with PEX or cyclophosphamide, though I have heard of some having methylprednisolone or other immunomodulating drugs. Again all with limited success. 7b I believe I share the view of most patients with C3G and their families. There is nothing available for patients that actually targets the relevant components of complement. Patients who require treatment receive something usually ineffective and end up on dialysis anyway. There has been a lot of frustration at this, but recently I think there is more hope. Many are like me – following the development of these new drugs. We hear the accounts of patients who have been in trials. We hear how well the patients are doing. We hear from the experts, and we feel the optimism in the whole community.
8. If there are disadvantages for patients of current NHS treatments for primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Since the treatments don't target the underlying disease, the main disadvantage is that patients usually progress to ESRD and need dialysis. The strong immunosuppressives come with the side effect of making the patient much more susceptible to infections. Treatments for hypertension and lipid control are generally well tolerated with minimal side effects. Some infusions will require hospital admission for administration which will have significant impacts on a patient's life.

Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

9a. If there are advantages of primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	As above, medications for hypertension control and lipid control are usually well tolerated. They are oral agents and easy to take. 9c Assume the question should be if pegcetacoplan(PEG) overcome disadvantages? PEG is a targeted treatment which would prevent patients progressing to ESRD and needing dialysis.
10. If there are disadvantages of primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis over current treatments on the NHS please describe these. For example, are there any risks with pegcetacoplan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have not heard of any side effects or tolerance issues with PEG. I have heard about the administration methods, and I am curious to know more. I have heard that it is given as a subcutaneous infusion. This leads me to some concerns about differences in users and sites and as such doses. I admit I do not know enough to raise any serious concerns but would be interested to hear from others with more experience with PEG.
11. Are there any groups of patients who might benefit more from pegcetacoplan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	Patients with C3G or IC-MPGN tend to have varying levels of aggression in their disease progression. Some progress to ESRD in a few months, some up to a few years and some seem to have a slow burn over many years. PEG may have more benefit to patients with more aggressive disease, as this is more likely to be diagnosed earlier and monitored more closely. As such they would be found to be suitable and gain benefit from PEG.

Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

dexterity or cognitive impairments) that affect the suitability of different treatments	Patients that deteriorate over a long time may have delayed diagnosis, or less frequent monitoring and may not be deemed appropriate for PEG. I don't anticipate issues with PEG related to other health conditions. Patients tend to be younger and primary renal with other conditions secondary in my experience. There may be differences in access for native/transplant patients. Dialysis patients would likely not receive PEG. PEG interactions with other treatments should be identified by manufacturer or clinical experts.
12. Are there any potential equality issues that should be taken into account when considering primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis and pegcetacoplan? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	Nothing regarding the listed groups comes to mind. All I would think relevant is the varying levels of understanding of C3G/IC-MPGN amongst doctors. Most 2' or 3' renal centres for renal medicine should have understanding of the diseases and new treatments. I wonder if more rural areas with more focus on 1' care would be disadvantaged in receiving treatment with PEG? I also know from experience that since the diseases are rare, and doctors don't necessarily know everything about the conditions, patients must advocate for themselves. I know I have to prompt my doctors to check certain things, and that they aren't following every development in new treatments like PEG. Patients less able to educate themselves may be at a disadvantage, such as the elderly, the isolated and those without good support structures. Lower

Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Find more general information about the Equality Act and equalities issues here.	socioeconomic status groups, and others with generally lower medical literacy may suffer the same disadvantages.
13. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- C3G/IC-MPGN currently have no effective or targeted treatments.
- Pegcetacoplan is an effective, targeted treatment for C3G/IC-MPGN.
- Currently, patients progress to ESRD and require dialysis and transplants; expensive interventions which have massive impacts on health and QoL.
- Pegcetacoplan could prevent patients needing dialysis and transplantation.
- Pegcetacoplan would provide much needed, and deserved, hope and relief to patients and families who currently face an incurable and untreatable disease.

Thank you for your time.

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Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Single Technology Appraisal

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Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

Part 1: Living with this condition or caring for a patient with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis

Table 1 About you, primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis, current treatments and equality

1. Your name	Lewis Brimble
2. Are you (please tick all that apply)	☒ A patient with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	MPGN/DDD Support Group
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Other's experiences ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☒ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis? If you are a carer (for someone with primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis) please share your experience of caring for them	I first became unwell with C3G in 2010, at age nine, in the absence of any comorbidities or other past medical history. This is, unfortunately, a common age at first presentation. The disease took only two months to damage the kidneys enough for me to require dialysis. At this time, it took a considerable amount of time to receive a correct diagnosis due to knowledge of the disease being minimal, even among nephrologists. After a period of haemodialysis, I commenced peritoneal dialysis and returned home after three months in hospital, while my Mother began the work-up to donate her kidney. My clearance was not good on dialysis and I was chronically nauseated and fatigued, causing me to miss most of the remainder of primary school. After 18 months on dialysis, I received my transplant, and despite significant post-operative complications whilst still an inpatient, I returned home after four months in hospital with a healthy kidney. I was aware that the disease was recurrent, and would eventually return, however I did not expect this to happen a mere 18 months after my transplant, when my bloods were deranged at a routine follow-up appointment, and the resulting diagnostic biopsy showed some crescents on the sample. Although I was asymptomatic, it was at this point that it became clear that due to the disease and the lack of drug treatments at the time, that the clock had begun ticking, and it would only be a matter of time until I would be back on dialysis. This process took five years, during which time I was closely monitored, and was briefly treated with

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	Eculizumab, which had some positive effects, albeit temporarily. I began taking ACE-inhibitors, and later diuretics to slow the process and manage symptoms. The process of slowly deteriorating is mentally, as well as physically, taxing. The bad memories of my previous period of dialysis were still fresh in my mind, and the inevitability of this was clear. I had hope to begin medical school, and I was preparing to sit the entrance exams and writing my application when I once more, became too unwell to attend school. I recommenced dialysis a few months later, just after my 18th birthday. I was not able to sit my A levels, due to missing so much of my final year, so I left education at 18, on dialysis, and without the qualifications I'd worked so hard to achieve in order to enter medicine. This was extremely difficult for me mentally. My second period of dialysis was haemodialysis in hospital, which gave me a better quality of life than peritoneal dialysis due to a better clearance. However, it remained very disruptive to my life, as I could only work four days a week on non-dialysis days. Some haemodialysis patients feel their worst just before a session, when the level of toxins in their bodies are highest, and some patients feel worse afterwards, due to the effects of the dialysis itself. I always felt unwell after a session, so most of the remainder of those days were spent at home with malaise, a headache or muscle cramp. During the 18 months that I spent on dialysis, while my Father was worked-up to donate his kidney, I felt extremely stuck in my situation. I could not re-enter education, go abroad, or exceed my fluid limit of 1.5l per day, at a time when I was 18 years old and trying to enjoy myself with my friends. Whilst on dialysis, I became very unwell in 2018, from infective endocarditis, from my dialysis line. This required open heart surgery to remove the line and the vegetative mass from my heart. Furthermore, in the following weeks, I developed multiple pulmonary emboli, likely due to the cardiothoracic surgery. This delayed my transplant while I received anticoagulation. These complications, while uncommon, were a direct result of being on dialysis, due to C3G. I received my second transplant from my Dad in December 2019, at age 19. For the most part, post-operatively, I was much more straightforward this time, and began

Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

	taking Iptacopan a couple of months after the surgery, remaining on it ever since. I entered the phase two study and remain on the extension study. Five and a half years on, my bloods, urine and last biopsy look very good and I hope that I remain well for as long as possible. After some time spent working in the NHS, while completing a level three qualification as a substitute for A levels, I am now nearing completion of my paramedic science honours degree. I know that another period of dialysis, hopefully followed by a transplant, is inevitable. I was extremely lucky to have two parents who were willing, and able to donate to me. However my kidney is 54 years old, so will not live forever. I hope that C3G is not the reason for this, but it is the reason that I have spent the last 15 years in and out of hospital. I have been told that another transplant may not be possible due to the amount of abdominal scar tissue I have from previous surgeries, so I am very hopeful that this treatment continues to be effective. If there is one thing that I've learnt from this experience, is that serious illness can be just around the corner, and nothing is for certain, so I live my life accordingly, taking every opportunity, improving myself and helping others.
7a. What do you think of the current treatments and care available for primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I do not know of any other treatments specific to C3G that are currently available on the NHS. There is no cure for C3G. My use of Eculizumab was off-label. In the absence of drug treatments, the only treatments are dialysis and transplant, which do not treat the disease whatsoever, and do not prevent its recurrence.
8. If there are disadvantages for patients of current NHS treatments for primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The lack of available drug treatments is a disadvantage in itself, as in the absence of treatment, the disease will inevitably lead to end-stage renal failure. The duration of this deterioration may differ however the inevitability remains. Dialysis provides a poor quality of life, due to the time spent receiving treatment (typically four hours, three times a week + time spent putting on/taking off from the machine + travel time if in hospital). As previously mentioned, patients may still feel

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	unwell for long periods of time on dialysis, and be fluid and diet restricted as the machine cannot remove these things as well as a kidney would. Furthermore, long periods of dialysis are associated with a lower life expectancy. A transplant, albeit a major surgical procedure with dozens of post-operative follow-up appointments, eventually provides a far superior quality of life to dialysis, as most patients should lead a relatively normal life when transplanted. The only exception being that they are required to take lifelong immunosuppression medication, which makes them more susceptible to communicable disease. However, transplant is not a cure and does not have any effect on the disease activity. As soon as a person is transplanted, C3G is already working to damage the kidney, until it is no longer functioning.
9a. If there are advantages of pegcetacoplan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does pegcetacoplan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	Pegcetacoplan allows the patient to avoid dialysis and live a normal life, without the emotional toll that arises from knowing that any kidney is deteriorating as a result of C3G, and the physical toll as this process occurs. This should allow the patient to continue to work, perform activities of daily living, and care for others.
10. If there are disadvantages of pegcetacoplan over current treatments on the NHS please describe these. For example, are there any risks with pegcetacoplan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Pegcetacoplan would be the first recommended treatment for this disease, which would overcome the disadvantage of there being no effective treatments currently available. I have not heard of any serious adverse effects associated with pegcetacoplan, however it is known that the risk of meningitis is higher when using this treatment. This is well known and can be mitigated with immunisations and prophylactic

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	antibiotics, and a low threshold for seeking medical attention when unwell.
11. Are there any groups of patients who might benefit more from pegcetacoplan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I do not feel that patients currently on dialysis would benefit as much from Pegcetacoplan as their kidneys are already damaged to the point that dialysis is required. Consequently, preventing further kidney damage may not be beneficial. Patients who have C3G who still have their native kidneys, and have not yet reached the point of requiring dialysis, and patients with C3G who have received a transplant, would benefit the most from Pegcetacoplan, as they are all slowly deteriorating as the disease progresses. As the treatment is via a subcutaneous injection, it may be difficult for some patients to self-administer, however as the dosage is approx. twice per week, I anticipate that patients would be able to receive the treatment from a medical professional.
12. Are there any potential equality issues that should be taken into account when considering primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis and pegcetacoplan? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Knowledge of the condition among nephrologists has improved in the 15 years that I have been associated with the disease. However, there are still doctors who are not aware of the condition, or any associated treatments. This differs depending on the geographical location of the patient. Unfortunately, I have found that sometimes, many patients, including the elderly, who may not have access to the internet, are also under-informed as to the condition they have and the fact that there are potential new treatments in the pipeline. I have always been vocal about my condition with my clinicians and we encourage this among all patients with C3G, however I believe that more awareness is needed among nephrologists and patients about the disease and Pegcetacoplan.

Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

13. Are there any other issues that you would like the committee to consider?

N/A

Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- C3G currently has no cure or effective treatments, except dialysis and transplant, which merely delay end-stage renal failure and do not target the specific mechanism of the disease.
- C3G is extremely disruptive to patient's lives, as not only will it lead to the requirement of dialysis, but the gradual deterioration is physically, mentally and emotionally difficult for patients and their families.
- In the absence of disease-specific treatment, dialysis can result in other complications, leading to a lower quality of life, and increasing the financial burden on the NHS.
- Pegcetacoplan has the potential to prevent other patients from requiring dialysis, an expensive treatment that holds a low quality of life, whether they have their native kidneys or have been transplanted.

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Patient expert statement

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]



in collaboration with:

Erasmus School of
Health Policy
& Management



Maastricht University

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

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Huiqin Yang acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong also acted as project lead as well as health economist on this assessment and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Teresa Holly, Bradley Sugden, and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott and Maria Katsipataki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk and Keith Nockels critiqued the search methods in the submission and contributed to the writing of the report. Huiqin Yang and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
ACIP	Advisory Committee on Immunization Practices
ACP	American College of Physicians
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of Covariance
ARB	Angiotensin receptor blocker
ASN	American Society of Nephrology
ATC	Anatomical Therapeutic Chemical classification
BLQ	Below the limit of quantification
BMI	Body mass index
BNF	British National Formulary
C3	Complement 3
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA	Canada's Drug Agency
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CENTRAL	Central Register of Controlled Trials
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CS	Company submission
CV	Cardiovascular
DARE	Database of Abstracts of Review of Effects
DDD	Dense deposit disease
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSP	Disease Specific Programme
DSU	Decision Support Unit
EAG	External Assessment Group
ECM	Established clinical management
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimension-3 Levels
EQ-5D-5L	European Quality of Life-5 Dimension-5 Levels
ERA	European Renal Association
ESKD	End stage kidney disease
ESRD	End-stage renal disease
EU CTR	European Clinical Trials Register
EUR	Erasmus University Rotterdam
EY	Exposure year
FACIT	Functional Assessment of Chronic Illness Therapy
FMU	First morning urine
GFR	Glomerular filtration rate
GP	General Practitioner
HCRU	Healthcare Resource Utilisation

HD	Haemodialysis
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
HUI	Health Utilities Index
ICE	Intercurrent event
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
IC-MPGN	Immune-complex membranoproliferative glomerulonephritis
ICTRP	International Clinical Trials Registry Platform
IgA	Immunoglobulin A
iNHB	Incremental net health benefit
IPTA	Iptacopan
IQR	Inter quartile range
IRP	International Recognition Procedure
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDQOL	Kidney Disease Quality of Life
KRT	Kidney replacement therapy
KSR	Kleijnen Systematic Reviews
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LS	Least-square
MD	Mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MMF	Mycophenolate mofetil
MMRM	Mixed-effect model for repeated measures
MPGN	Membranoproliferative glomerulonephritis
N/A	Not applicable
NHB	Net Health Benefit
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	The Netherlands
NR	Not reported
OLP	Open label period
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Peritoneal dialysis
PD	Pharmacodynamics
PEG	Pegcetacoplan
PGIC	Patient Global Impression of Change
PICOS	Population, Interventions, Comparisons, Outcomes, and Study design
PK	Pharmacokinetics

PNH	Paroxysmal Nocturnal Haemoglobinuria
PP	Per-protocol set
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
Q1	First quartile
Q3	Third quartile
QALY	Quality-adjusted life year
QoL	Quality of life
RaDaR	Rare Disease Registry
RAS	Renin-angiotensin system
RCP	Randomised controlled period
RCT	Randomised controlled trial
RD	Risk difference
RoB	Risk of bias
ROBINS-I	Risk Of Bias In Non-Randomized Studies - of Interventions
RWE	Real world evidence
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	36-item Short Form Health Survey
SGLT2	Sodium-glucose cotransporter-2
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SoC	Standard of care
SOC	System Organ Class
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment emergent adverse event
UK	United Kingdom
UKRR	United Kingdom Renal Registry
UMC+	University Medical Center+
uPCR	Urinary protein to creatinine ratio
US	United States
WCN	World Congress of Nephrology
WHO	World Health Organization
WPAI	Work Productivity and Impairment
WTP	Willingness to pay
Vs	Versus

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1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID 6489	Summary of issue	Report Sections
1	Lack of evidence on CKD stages 4 and 5	2.1
2	Lack of evidence for comparison with eculizumab	2.3
3	Possible treatment effect waning for pegcetacoplan plus standard of care (SoC) versus SoC	3.2
4	Baseline C3 level is a potential treatment effect modifier	3.2
5	Potential heterogeneity in the indirect treatment comparison (ITC)	3.3
6	Differences between ITC trials in standard of care	3.3
7	Inclusion of a stable disease health state	4.2.2 & 4.2.6
8	Inclusion of costs and benefits outside of the NHS and personal social services (PSS)	4.2.5
9	Use of unequal follow-up durations (52 weeks vs 26 weeks) in treatment effect estimation	4.2.6
10	Use of two separate regression models for the estimation of uPCR state transitions and eGFR decline. with limited data and validity	4.2.6
11	Identical transition probabilities before and after transplant	4.2.6
12	Issues related to the VALIANT health-related quality of life data and methods to inform CKD stage 1 and 2 utility values	4.2.8
13	Validity of the chosen CKD stage 3-5, and dialysis utility values	4.2.8
14	Exclusion of pegcetacoplan administration costs	4.2.9
15	Limited validation of the economic model	5.3
CKD = chronic kidney disease; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; ITC = indirect treatment comparison; NHS = National Health Service; PSS = personal and social services; SoC = standard of care; uPCR = urinary protein to creatinine ratio		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased time to disease progression with incremental QALYs gained in early chronic kidney disease (CKD) stages 1 and 2 of [REDACTED] versus standard of care (SoC) and [REDACTED] versus iptacopan + SoC.

Overall, the technology is modelled to affect costs by:

- Increased acquisition costs versus SoC with incremental costs of [REDACTED], and reduced acquisition costs versus iptacopan + SoC with incremental costs of [REDACTED].
- Reduced dialysis and transplant costs with incremental costs of [REDACTED] versus SoC and [REDACTED] versus iptacopan + SoC.

The modelling assumptions that have the greatest effect on the ICER are:

- Assuming treatment discontinuation in the stable disease health state. Removing treatment discontinuation in the stable disease health state in a scenario analysis increased the company ICER for pegcetacoplan +SoC to [REDACTED].
- The inclusion of a stable disease health state. Removing the stable disease health state in a scenario analysis increased the company ICER for pegcetacoplan +SoC to [REDACTED].
- The inclusion of cost savings and QALY gains associated with the reallocation of kidneys no longer required by patients treated with pegcetacoplan or iptacopan. Removing these cost savings and QALY benefits in a scenario analysis increased the company ICER for pegcetacoplan +SoC to [REDACTED].

The EAG notes that those results and issues related to the comparison with iptacopan can now be regarded as irrelevant given the withdrawal of iptacopan from its appraisal.

1.3 The decision problem: summary of the EAG's key issues

Table 1.2: Key issue 1: Lack of evidence on CKD stages 4 and 5

Report Section	Section 2.1
Description of issue and why the EAG has identified it as important	The company stated that patients with CKD stage 4 and stage 5 were excluded from the key trial, VALIANT, which implies a lack of generalisability to such patients in clinical practice.
What alternative approach has the EAG suggested?	The EAG suggested that these patients might be excluded from the decision problem. Although the company responded in such a way that suggested they wished to retain them as long as they were not on dialysis or post-transplant, they clarified in the FAC that they: <i>“do not anticipate patients in CKD 5 would continue to receive pegcetacoplan, instead these patients would be prepared to initiate renal replacement therapy.”</i> They also provided some outcome data for the three patients (3%) who had CKD stage 4 in VALIANT, having progressed post-screening.

Report Section	Section 2.1
	The EAG agrees with the company that inference based on such a small sample is limited.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Patients with CKD stage 4 and 5 could be excluded from recommendation if no further evidence can be found of the clinical and cost-effectiveness of pegcetacoplan for this subgroup.
CKD = chronic kidney disease; EAG = External Assessment Group	

Table 1.3: Key issue 2: Lack of evidence for comparison with eculizumab

Report Section	Section 2.3
Description of issue and why the EAG has identified it as important	The company stated that eculizumab was excluded from the base-case analysis due to limited evidence on its use in clinical practice and lack of robust data on eGFR and uPCR in C3G. However, no evidence for eculizumab was provided.
What alternative approach has the EAG suggested?	The EAG requested evidence as to the number of patients who have received eculizumab in clinical practice, as well as a full systematic review and comparison with pegcetacoplan. The company reported that only seven patients had received it since NHS England allowed its use for the subgroup of highly aggressive post-transplant recurrence and until 2023. They stated that a new systematic review was not possible but listed seven studies from one that they had already conducted. However, descriptions of these studies did not permit their evaluation by the EAG. They also stated that eculizumab had been excluded as a comparator in the iptacopan appraisal, which the EAG confirmed had been reported in the draft guidance. However, the EAG understood that this was on the basis of iptacopan being prescribed earlier than eculizumab post-transplant, which is not currently standard of care.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	This might have depended on whether iptacopan was recommended i.e., if it had been, then the EAG understand from the iptacopan draft guidance that eculizumab will no longer be prescribed. However, given that iptacopan will not be recommended and thus become standard of care then evidence of the comparison between pegcetacoplan and eculizumab might be useful.
C3G = C3 glomerulopathy; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; NHS = National Health Service; uPCR = urinary protein to creatinine ratio	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.4: Key issue 3: Possible treatment effect waning for pegcetacoplan plus SoC vs SoC

Report Section	Section 3.2
Description of issue and why the EAG has identified it as important	Improvement in the primary outcome, log-transformed FMU uPCR, appears to be maintained at the 26-week randomised controlled period, and up to at least 52 weeks. However, it appears that there is a gradual reduction in the improvement in outcomes for those randomised to pegcetacoplan in VALIANT after the end of the randomised controlled period of 26 weeks. This includes eGFR, where the change from baseline is -1.49 ($-5.89, 2.89$) at 26 weeks, and -3.65 (-8.93 to 1.62) at 52 weeks. This is despite the company claiming that: "... eGFR remained stable in the pegcetacoplan-to-pegcetacoplan group through 52 weeks." It is therefore possible that the treatment effect (i.e., difference in outcomes between pegcetacoplan and placebo) might also diminish if patients in the placebo arm had continued on placebo, although this has not been tested because of switching to pegcetacoplan.
What alternative approach has the EAG suggested?	Relevant scenario analyses should be conducted to assess the impact of treatment waning on the assessment of cost-effectiveness.
What is the expected effect on the cost effectiveness estimates?	The ICER might increase if some treatment waning was to be assumed.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that relevant scenario analyses should be conducted to assess the impact of treatment waning on the assessment of cost-effectiveness.
EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; FMU = first morning urine; ICER = incremental cost-effectiveness ratio; SoC = standard of care; uPCR = urinary protein to creatinine ratio	

Table 1.5: Key issue 4: Baseline C3 level is a potential treatment effect modifier

Report Section	Section 3.2
Description of issue and why the EAG has identified it as important	Based on the subgroup analyses of the VALIANT trial, the results of subgroup analysis in terms of disease, age or transplant status were generally consistent with the results of primary analyses. However, it should be noted that based on the results of subgroup analyses in terms of baseline C3 level, there were significant differences in the outcomes of proteinuria and eGFR at week 26 between the subgroup of baseline low C3 level and the subgroup of baseline normal C3 level. This means that baseline C3 level is a potential treatment effect modifier. Given that baseline C3 level is a potential treatment effect modifier, the company did not conduct relevant scenario analyses for the assessment of cost effectiveness.
What alternative approach has the EAG suggested?	As baseline C3 level is a potential treatment effect modifier, this should be carefully considered in the economic model. Relevant scenario analyses should be conducted for the assessment of cost effectiveness.

Report Section	Section 3.2
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that, given that baseline C3 level is a potential treatment effect modifier, this should be carefully considered in the economic model. Relevant scenario analyses should be conducted for the assessment of cost effectiveness.
C3 = complement 3; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate	

Table 1.6: Key issue 5: Potential heterogeneity in the ITC

Report Section	Section 3.3
Description of issue and why the EAG has identified it as important	There appeared to be no formal assessment of suitability of trials for pooling, and one relevant RCT (NOBLE) was excluded.
What alternative approach has the EAG suggested?	The EAG requested consideration of its inclusion, to which the company responded that there were a number of differences with the included trials, VALIANT and APPEAR-C3G. The EAG agrees that its exclusion was justifiable based on the combination of these differences. However, one of them is that all patients were post-transplant, whilst those in APPEAR-C3G all have native disease, as do most of those in VALIANT, but the company themselves argue that transplant status makes no difference to the treatment effect based on subgroup analyses of VALIANT, which the EAG can confirm appears to be the case. Also, any effect of transplant status raises the question as to whether the small number of post-transplant patients should be removed from VALIANT for its inclusion in the ITC, albeit that any effect is probably small and therefore the effect of this would also be very small.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	NOBLE could be included in the ITC, and/or the post-transplant patients could be removed from the ITC. This uncertainty does also raise a question about the applicability of the evidence for the post-transplant subgroup. This issue can probably be regarded as resolved in light of the withdrawal of the iptacopan appraisal.
EAG = External Assessment Group; ITC = indirect treatment comparison; RCT = randomised controlled trial	

Table 1.7: Key issue 6: Differences between ITC trials in standard of care

Report Section	Section 3.3
Description of issue and why the EAG has identified it as important	It was unclear how large any differences in standard of care might be between the trials in the ITC, and the effect that such differences might have on the outcomes.
What alternative approach has the EAG suggested?	The EAG requested clarification from the company, who responded that they considered that any difference would probably not have a substantial impact on the results of the ITC. They also provided a comparison of types of standard of care,

Report Section	Section 3.3
	which showed that the most prominent difference was in immunosuppressant use with much greater use in VALIANT than in APPEAR-C3G. They also stated that there was evidence that the effectiveness of iptacopan was reduced by adding it to immunosuppressant use, citing an EMA report, but that this was not the case with pegcetacoplan. The EAG can confirm that subgroup analyses of VALIANT data showed that the treatment effect on proteinuria and eGFR change was still substantial and significant with immunosuppressant therapy.
What is the expected effect on the cost effectiveness estimates?	The ICER would probably be lower without the differences in standard of care.
What additional evidence or analyses might help to resolve this key issue?	There are probably no further analyses that can be conducted given lack of access to iptacopan data. This issue can probably be regarded as resolved in light of the withdrawal of the iptacopan appraisal.
EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; EM = European Medicines Agency; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the issue tables below.

Table 1.8: Key issue 7: Inclusion of a stable disease health state

Report section	4.2.4 & 4.2.6
Description of issue and why the EAG has identified it as important	The company's model includes a stable disease health state. This health state lacks clinical rationale and empirical justification, appears structurally redundant, and introduces structural complexity.
What alternative approach has the EAG suggested?	Various scenario analyses related to the definition and duration of stable disease, the probability of disease stabilisation, eGFR decline and treatment discontinuation during stable disease, as well a scenario analysis assuming no stable disease occurring in either treatment strategy.
What is the expected effect on the cost effectiveness estimates?	The company's scenario analyses defining stable disease as uPCR <0.3 g/g and restricting the VALIANT data to 26 week of follow-up to estimate the probability of disease stabilisation reduced the ICER versus SoC, whereas all other scenario analyses provided by the company in response to clarification increased the ICER versus SoC. The most impactful scenario analyses were 1) no treatment discontinuation during stable disease (ICER versus SoC of £335,344) and 2) assuming no stable disease occurs for either treatment strategy (ICER versus SoC of £272,573).
What additional evidence or analyses might help to resolve this key issue?	Clinical justification and ideally empirical evidence to support the necessity and validity of including a stable disease health state.

Report section	4.2.4 & 4.2.6
EAG = evidence assessment group; eGFR = estimated glomerular filtration rate; ICER = incremental cost-effectiveness ratio; SoC = standard of care; uPCR = urinary protein to creatinine ratio	

Table 1.9: Key issue 8: Inclusion of costs and benefits outside of the NHS and Personal Social Services (PSS)

Report section	4.2.5
Description of issue and why the EAG has identified it as important	The company included cost savings and QALY gains associated with the reallocation of kidneys no longer required by patients treated with pegcetacoplan or iptacoplan to other NHS patients. These cost savings and health benefits accruing to patients outside the C3G/IC-MPGN population represent indirect effects which are not directly attributable to the intervention's impact on the treated population (or their carers) and hence fall outside the scope of the NICE reference case, which specifies a perspective limited to the NHS and PSS.
What alternative approach has the EAG suggested?	Analyses excluding cost savings and QALY gains associated with the reallocation of kidneys no longer required by patients treated with pegcetacoplan or iptacoplan. Presenting any benefits and cost-savings from kidney reallocation in a disaggregated format, separately from the reference-case results, including a detailed overview and elaboration of the assumptions and uncertainties related to this estimation.
What is the expected effect on the cost effectiveness estimates?	The company's scenario analysis excluding cost savings and QALY gains associated with the reallocation of kidneys substantially increased the ICER versus SoC to £165,388 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	N/A
C3G = C3 glomerulopathy; EAG = evidence assessment group; ICER = incremental cost-effectiveness ratio; IC-MPGN = immune-complex- membranoproliferative glomerulonephritis; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year; SoC = standard of care	

Table 1.10: Key issue 9: Use of unequal follow-up durations (52 weeks vs 26 weeks) in treatment effect estimation

Report section	4.2.6
Description of issue and why the EAG has identified it as important	In the company's base-case, baseline and 26-week data (randomised period) were used to inform outcomes for the SoC arm, while baseline and 52-week data (randomised plus open-label period) were used for pegcetacoplan + SoC. This asymmetric use of follow-up data allows a longer observation period for pegcetacoplan, during which further improvement or regression to the mean may occur. As a result, part of the observed difference between arms may reflect unequal observation windows rather than true treatment effect. This introduces potential upward bias in estimated treatment benefit and undermines comparability.
What alternative approach has the EAG suggested?	To align the comparison, both arms should be modelled using data from the same follow-up duration (i.e., baseline to 26 weeks),

Report section	4.2.6
	corresponding to the randomised controlled period of the VALIANT trial.
What is the expected effect on the cost effectiveness estimates?	Restricting both arms to equal follow-up (26 weeks) might reduce the estimated relative treatment effect of pegcetacoplan and increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	• Re-estimation of treatment effects using 26-week data for both arms for all treatment effect parameters used in the health economic model. • Adding scenario analyses testing the impact of using 52-week versus 26-week data for treatment effect estimation.
EAG = evidence assessment group; ICER = incremental cost-effectiveness ratio; SoC = standard of care	

Table 1.11: Key issue 10: Use of two separate regression models for the estimation of uPCR state transitions and eGFR decline with limited data and validity

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The company estimated two separate regression models (one for uPCR and one for eGFR) based on limited trial data (baseline and one follow-up per arm). This approach does i) not fully exploit longitudinal information available in the VALIANT trial and ii) may result in double counting of treatment effects inflating the estimated overall effect of pegcetacoplan + SoC. Moreover, based on predicted values and diagnostics of the regression models, both have limited (clinical) validity. Collectively, this limits confidence in the estimated treatment effects and the credibility of (extrapolated) outcomes.
What alternative approach has the EAG suggested?	A single, integrated regression framework jointly modelling uPCR and eGFR (or a sequential model with uPCR as a predictor of eGFR) using all available repeated measures. Diagnostics such as residual plots, goodness-of-fit statistics and scenario analyses should be presented to assess model robustness. As well as adopting a simpler modelling approach, i.e. model structure, such as in GID-TA11331; iptacopan for treating C3G, requiring more straight forward statistical models.
What is the expected effect on the cost effectiveness estimates?	Reducing potential double counting would likely decrease the estimated treatment benefit for pegcetacoplan, resulting in higher ICERs.
What additional evidence or analyses might help to resolve this key issue?	• Re-estimation using all longitudinal trial data. • Exploration of model structures consistent with prior NICE appraisals in C3G.
C3G = complement 3 glomerulopathy; EAG = evidence assessment group; eGFR = estimated glomerular filtration rate; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; SoC = standard of care; uPCR = urinary protein to creatinine ratio	

Table 1.12: Key issue 11: Identical transition probabilities before and after transplant

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The company assumed identical transition probabilities before and after transplant. This assumption lacks clinical plausibility and may underestimate post-transplant morbidity and mortality, biasing long-term cost effectiveness estimates.

Report section	4.2.6
What alternative approach has the EAG suggested?	Differentiating post-transplant transition probabilities and outcomes from pre-transplant ones, informed by registry data, published studies, or clinical expert elicitation. A simpler approach, for the post-transplant phase, as used in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy) would have been preferred and might have allowed the use of external post-transplant data.
What is the expected effect on the cost effectiveness estimates?	Increasing post-transplant morbidity and would likely decrease the estimated treatment benefit for pegcetacoplan, resulting in higher ICERs.
What additional evidence or analyses might help to resolve this key issue?	• Use of registry or real-world data on post-transplant outcomes in C3G. • Using a simpler approach for the post-transplant phase, as used in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy), potentially in combination with external post-transplant data. • Scenario analyses varying post-transplant transition probabilities and mortality risks. • Validation of post-transplant assumptions by clinical experts.
C3G = complement 3 glomerulopathy; EAG = evidence assessment group; ICER = incremental cost-effectiveness ratio	

Table 1.13: Key issue 12: Issues related to the VALIANT health-related quality of life data and methods to inform CKD stage 1 and 2 utility values

Report section	4.2.8
Description of issue and why the EAG has identified it as important	Pooled VALIANT data informed the utility value for a joint CKD stage 1 and 2, yet differentiated by uPCR levels smaller or higher than 1g/g. The EAG is concerned that 1) the few measurement points might not reflect the course of the disease; 2) it constitutes a mismatch with the health economic model structure which differentiates by additional uPCR levels and treats CKD stages separately; 3) the methods used to derive the utility values are questionable, namely the use of linear regression techniques and the lack of missing data assessment and imputation; and 4) uncertainty analyses were informed by 20% of the deterministic value instead of standard errors from regressions.
What alternative approach has the EAG suggested?	The EAG has suggested to align the HRQoL regression model structure with the CS health economic model (2) using more refined regression approaches, i.e., mixed models for repeated measures, while also considering interaction effects, supported by good practice diagnostics (e.g., visualisations) (3), an in-depth assessment of missing data and adequate imputation techniques (3), as well as to use the standard errors from regressions in uncertainty analyses (4).
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses	During clarification stage, the EAG requested the company to align the HRQoL regression model with the CS health economic model structure, provide further assessment of missing data in VALIANT

Report section	4.2.8
might help to resolve this key issue?	and exploration of imputation, and consecutively use mixed effects regression models to appropriately incorporate longitudinal data.
CKD = chronic kidney disease; CS = company submission; EAG = External Assessment Group; HRQoL = health-related quality of life; uPCR = urinary protein to creatinine ratio	

Table 1.14: Key issue 13: Validity of the chosen CKD stage 3-5 and dialysis utility values

Report section	4.2.9
Description of issue and why the EAG has identified it as important	The EAG questions the validity of the literature-based CKD stage 3-5 and dialysis utility values. For CKD stages 3-5, Sidhu et al. (2024) had several shortcomings, in particular small sample size and the EQ-5D-5L mapped with the US value set. For dialysis, the EAG questions the relatively low literature-based utility values, potentially resulting from age-related comorbidities in the older, wider CKD population in the study by Lee et al. (2005) reported in the SLR by Cooper et al. (2020) as compared to the modelled CS population.
What alternative approach has the EAG suggested?	The EAG requested cross-validation with utility values from the literature and scenario analyses exploring these. Faced with limited evidence in the CS population, the EAG used utilities from GID-TA11331 (i.e., APPEAR C3G, Jesky et al. 2016, Lee et al. (2005)) adjusted in that submission for the C3G population in its base-case.
What is the expected effect on the cost effectiveness estimates?	Using higher CKD stage 3-5 and dialysis utility values based on GID-TA11331 (i.e., APPEAR C3G, Jesky et al. 2016, Lee et al. 2005), in the EAG base-case resulted in an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	Analyses of additional (patient-level) EQ-5D data on CKD stage 3+ C3G/IC-MPGN patients, as well as age- and gender adjustments of literature-based utility values for the CS patient population might help to resolve this key issue.
C3G = complement 3 glomerulopathy; CKD = chronic kidney disease; CS = company submission; EAG = External Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; ICER = incremental cost-effectiveness ratio; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; SLR = systematic literature review; US = United States	

Table 1.15: Key issue 14: Resource use and costs: Exclusion of pegcetacoplan administration costs

Report section	4.2.9
Description of issue and why the EAG has identified it as important	The CS does not include administration costs for pegcetacoplan, assuming that pegcetacoplan would be self-administered subcutaneously by all patients with use of a commercially available syringe system that would be provided by the company. However, the EAG clinical expert suggested that, whilst they are aware of self-administration as an option, patients were administered in-centre during clinical trials the expert was involved in.
What alternative approach has the EAG suggested?	The EAG requested evidence regarding the distribution of patients that would be administered i) by a healthcare professional and ii) by the patients or caregiver. Further, the EAG requested a scenario analysis incorporating administration costs for patients whose treatment was administered by a healthcare professional and the cost

Report section	4.2.9
	associated with providing instructions to patients that are self-administered (including the cost of the syringe system).
What is the expected effect on the cost effectiveness estimates?	Treatment administration in hospital is expected to increase the administration costs of pegcetacoplan and hence increase the ICER versus SoC.
What additional evidence or analyses might help to resolve this key issue?	Further supporting evidence as to the proportion of patients on pegcetacoplan that would be self-administered and receive doses in the hospital. A scenario analysis assessing the impact of assuming that all patients would receive all doses by a healthcare professional in a hospital.
CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; SoC = standard of care	

Table 1.16: Key issue 15: Limited validation of the economic model

Report section	4.2.9
Description of issue and why the EAG has identified it as important	Validation of the economic model was limited. Additional details/validation were requested but not provided, pertaining to: model programming validation conducted by a secondary health economist as stated in the CS, the completed TECH-VER checklist as requested, cross-validation compared with previous technology appraisals, and external validation to evidence (not) used to develop the economic model.
What alternative approach has the EAG suggested?	Internal validation: The EAG requested details regarding the tests and associated outcomes of the validation, as well as a completed TECH-VER checklist. Cross-validation: The EAG requested cross-validation to various TAs. External validation: The EAG requested external validation with reference to evidence (not) used to develop the economic model.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	The validation exercises as requested by the EAG in its clarification letter.
CS = company submission; EAG = evidence assessment group; TA = technology appraisal; TECH-VER = technical verification	

1.6 Summary of the EAG's view

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was £2,501,697 per QALY gained. [REDACTED]

[REDACTED]. The most influential adjustments were exclusion of the stable disease health state and kidney transplant opportunity costs and benefits. The ICER increased most in the scenario analysis with alternative assumptions regarding the stable disease health state.

In summary, there is large remaining uncertainty about the effectiveness and cost effectiveness of pegcetacoplan + SoC. Compared with other recent NICE appraisals in complement 3 glomerulopathy

(C3G) (i.e., GID-TA11331; iptacopan for treating complement 3 glomerulopathy), 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.

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People aged 12 years and older with primary C3G or primary IC-MPGN	People aged 12 years and older with primary C3G or primary IC-MPGN		The decision problem is in line with the NICE scope.
Intervention	Pegcetacoplan (Aspaveli)	Pegcetacoplan (Aspaveli)		The intervention is in line with the NICE scope
Comparator(s)	Established clinical management without pegcetacoplan, which may include: • Angiotensin converting enzyme inhibitors • Angiotensin II receptor antagonists • Corticosteroids • Mycophenolate mofetil • Sodium-glucose co-transporter-2 inhibitors (SGLT2) • Iptacopan (subject to NICE evaluation; in people older than 18 years, for C3G) • Other immunomodulatory treatments In people who have previously had a kidney transplant and who have highly aggressive C3 glomerulopathy recurrence as	Established clinical management without pegcetacoplan, which may include: • Angiotensin converting enzyme inhibitors • Angiotensin II receptor antagonists • Corticosteroids • Mycophenolate mofetil • SGLT2 inhibitors • Iptacopan (subject to NICE evaluation; in people older than 18 years, for C3G) • Other immunomodulatory treatments In people who have previously had a kidney transplant and who have highly aggressive C3 glomerulopathy recurrence as specified in the NHS England	Eculizumab is not included in the base-case analysis due to the limited evidence regarding its widespread use in clinical practise in the UK and lack of robust data confirming its efficacy in stabilising eGFR and reducing uPCR in patients with C3G.	A comparison with eculizumab should be made or that subgroup eligible for eculizumab should be excluded from the decision problem.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	specified in the NHS England clinical commissioning policy for eculizumab • Eculizumab	clinical commissioning policy for eculizumab • Eculizumab		
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	Stabilisation of deterioration in eGFR Reduction in proteinuria Disease progression (including need for kidney transplant and/or dialysis) Mortality Adverse effects of treatment Health-related quality of life		The outcomes reported are in line with the NICE scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	NR		Partly inconsistent with the reference case: • The company modelled cost savings and QALY gains by accounting for reallocation of kidneys no longer required for patients treated with pegcetacoplan or iptacopan to the wider NHS population (i.e. other patients on the NHS transplant waiting list). • US tariff used to inform the CKD 3-5 health state utilities

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • People who have and have not had a kidney transplant • People with C3G For people with C3G, further subgroups could include C3 glomerulonephritis, dense deposit disease and any specific genetic subtypes of these • People with primary IC-MPGN • Age (12 to 18 years or over 18 years)	People who have and have not had a kidney transplant People with C3G People with primary IC-MPGN Age (12 to 18 years or over 18 years) People on concomitant immunosuppression	Clinical data is provided on the subgroups listed in the scope. In addition to the subgroups listed in the final scope, the following subgroup has been included: People on concomitant immunosuppression All available and relevant information in relation to this subgroup is included in Section 1. The economic model was developed to analyse the subgroups of patients with C3G and primary IC-MPGN, and people on concomitant immunosuppression. However, there is no significant difference in results of the other subgroups, and therefore, the cost effectiveness would not be expected to be different.	Subgroup analyses were largely appropriate. However, although baseline C3 level is a potential treatment effect modifier, the company did not conduct relevant scenario analyses for the assessment of cost effectiveness.
Special considerations including issues related to equity or equality	None specified.	Sobi does not believe there are equality considerations that are likely to impact the recommendations and their appropriateness. However, the committee should consider whether the longer waiting		No comment.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		times faced by Black and Asian people represents a health inequality. A third of people (35 %) waiting for a kidney across the UK are from minority ethnic groups but in 2017/18, of those providing their ethnicity when registering on the NHS Organ Donor Register, only 3.3% were Asian, 1% were Black and 2% were mixed race. This may need to be factored in when considering who should be treated and when, to ensure all patients have the best chance.		
Based on Table 1 of the CS¹ C3G = complement 3 glomerulopathy; CKD = chronic kidney disease; CS = company submission; EAG = evidence assessment group; eGFR = estimated glomerular filtration rate; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; NR = not reported; QALY = quality-adjusted life year; SGLT2 = sodium-glucose cotransporter-2; uPCR = urinary protein to creatinine ratio; UK = United Kingdom; US = United States				

2.1 Population

The population in the National Institute for Health and Care Excellence (NICE) scope and the decision problem (DP) are the same i.e., People aged 12 years and older with primary C3 Glomerulopathy (C3G) or primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN).²

EAG comment: The company stated that:¹ *“Overall, the VALIANT and VALE studies were generally representative of a real-world C3G or primary IC-MPGN population with the exception of patients with CKD stages 4 or 5, who were excluded from the study based on their baseline eGFR being <30 ml/min per 1.73 m².”* Therefore, the company were asked to clarify if patients with chronic kidney disease (CKD) stages 4 or 5 were therefore excluded from the DP, to which they responded that:³ *“UK clinicians consulted by Sobi indicated they would consider pegcetacoplan in CKD stage 4 patients, particularly where there is evidence of active glomerular disease and no irreversible damage—i.e., where a treatment effect is plausible—or in patients who have demonstrated a response to pegcetacoplan but have slowly progressed from CKD stage 3.”* The company also clarified that there were in fact some patients in VALIANT with CKD stage 4, which were the 3% who progressed to stage 4 after screening. They also provide the urinary protein to creatinine ratio (uPCR) data for those three patients, one who had been treated with pegcetacoplan and two with placebo. Although the outcomes were better for the pegcetacoplan patient, the EAG consider the difference at 52 weeks to be very small, and the EAG agree with the company that inference is limited by the very small sample size.

The company also stated that: *“Broadly, UK clinicians would not recommend treating CKD stage 5 as the kidneys are likely to be irreversibly damaged, but this would be on a case by case basis as some patients could be on treatment and not on dialysis/transplant. [Personal correspondence, 7 October 2025].”*

In conclusion, it seems that the company would like to include patients with CKD stage 4, and those not on dialysis/transplanted with CKD stage 5. Given the lack of evidence for these patients, the EAG identify this as a key issue.

2.2 Intervention

The intervention in the NICE scope and the DP is pegcetacoplan.^{1,2} In the company submission (CS), it states:¹ *“...a submission to the EMA was made in February 2025 for the indication being assessed in this appraisal, for the treatment of primary C3G and primary IC-MPGN in people 12 years and over.*

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The dosing is:

- Adults of any weight and adolescents weighing ≥ 50 kg receive a subcutaneous (SC) infusion of 1,080 mg (20 mL) twice weekly.
- For adolescents weighing 35 to <50 kg, the first dose is 648 mg (12 mL), the second dose of 810 mg (15 mL), and the maintenance dose is 810 mg (15 mL) twice weekly. For those weighing 30 to <35 kg, the first and second doses are both 540 mg (10 mL) and the maintenance dose is 648 mg (12 mL) twice weekly.

EAG comment: Note that pegcetacoplan is intended to be given in addition to established clinical management (ECM), which is the comparator.

2.3 Comparators

The comparator in the DP is identical to that in the NICE scope i.e., a list of treatments that form ECM.¹

² However, the company excluded eculizumab, stating that:¹ *“Eculizumab is not included in the base case analysis due to the limited evidence regarding its widespread use in clinical practise in the UK and lack of robust data confirming its efficacy in stabilising eGFR and reducing uPCR in patients with C3G.”*

EAG comment: Note that although the list of treatments that form ECM in the DP is the same as that in the NICE scope, it is important to know the extent to which the mix of treatments given concomitantly in the clinical trials, VALIANT, NOBLE and APPEAR-C3G, resembles that in England and Wales clinical practice. This is discussed in Section 3.

Because no evidence was provided in the CS to validate the statement regarding eculizumab, the company were asked the following in the clarification letter:

- a) Please provide evidence of the number and percentage of patients currently being treated with eculizumab in England and Wales clinical practice for patients with post-transplant recurrence as specified in the National Health Service (NHS) England clinical commissioning policy for eculizumab.

They responded that only seven patients have been treated with eculizumab since the establishment of the NHS England commissioning policy in 2017, and until March 2023.³

- b) Please provide a systematic literature review (SLR) to show the range of evidence available for eculizumab in populations as similar as possible to that specified in the NHS England clinical commissioning policy for eculizumab.

They responded that there was insufficient time for an SLR, but listed five observational studies and a meta-analysis that were found in another SLR that they had conducted, but not submitted as part of the CS.³ Very few details of these studies were provided, and the population description lacked any information that would allow comparison to the population as described in the NICE scope i.e., whether people had previously had a kidney transplant and subsequently had highly aggressive C3 glomerulopathy recurrence (see Table 1). Some outcomes were reported, although they did not include measures of kidney function, which are the primary and secondary outcomes in VALIANT.

- c) If appropriate clinical effectiveness evidence is found, then please conduct a comparison with pegcetacoplan on all available outcomes.

They responded:³ *“Due to time constraints and committee agreement during the iptacopan appraisal that eculizumab is not an appropriate comparator, as well as the lack of eculizumab data, a comparison with pegcetacoplan was not deemed feasible.”*

It is indeed the case that eculizumab was excluded as a comparator as stated in the draft guidance for the iptacopan appraisal. This appears to be because clinical experts stated that it would not be prescribed given that iptacopan could be used earlier after transplant. However, as the EAG argued in the iptacopan appraisal, until there is a positive recommendation for iptacopan, currently standard of care (SoC) does not include iptacopan and later in the care pathway it does currently include eculizumab. Although it does appear that the evidence for eculizumab in C3G is limited, and that the number of patients in this subgroup in clinical practice is very small, for these patients no evidence of the comparison between pegcetacoplan and eculizumab has been provided. The EAG clinical expert also considers that it could be a comparator, albeit for a very small number of patients (see Appendix). This is therefore a key issue, which might be resolved if there is a positive recommendation for iptacopan.

It should be noted that, during the late stage of the appraisal of pegcetacoplan, the recent NICE guidance (published on 29 October 2025) stated that NICE was unable to make a recommendation on iptacopan for treating C3G in adults, because the company has withdrawn from the appraisal.⁴ Therefore, iptacopan is no longer included as a comparator for this appraisal of pegcetacoplan. Given that it happened during the late stage of the appraisal of pegcetacoplan, we have included the indirect treatment comparison (ITC) sections in the report for this appraisal of pegcetacoplan. This therefore has implications for Key Issues 5 and 6, which related to the ITC.

2.4 Outcomes

The outcomes in the DP are in line with those in the NICE scope.^{1,2}

EAG comment: None.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The company performed an SLR to identify and summarise the available randomised controlled trial (RCT) and other relevant evidence relating to the efficacy and safety of pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.¹ The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.⁵ The EAG has presented only the major limitations of each search strategy in the report.

Appendix B of the CS details an SLR conducted to identify relevant clinical evidence on efficacy and safety outcomes of treatments for C3G and primary IC-MPGN.⁶

EAG comment:

- An SLR was conducted to identify relevant clinical evidence on efficacy and safety outcomes of treatments for C3G and primary IC-MPGN.
- The CS, Appendix B and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 3, 6} Searches were conducted on 2 September 2024, and updated on 27 May 2025. Additional searches were conducted on 9 October 2025 in response to a request for clarification by the EAG.
- Relevant studies were identified by searching Embase, MEDLINE (including the Epub Ahead of Print, In-Process, In-Data Review & Other Non-indexed Citations, Daily and Versions segments of MEDLINE) and the Cochrane Central Register of Controlled Trials (CENTRAL). The Cochrane Database of Systematic Reviews (CDSR) was searched to identify relevant SLRs and meta-analyses.
- The conferences of the following five key organisations were reviewed for relevant abstracts between 2022 and 2025, through searches of congress websites or abstract books: American Society of Nephrology (ASN), European Renal Association (ERA), UK Kidney Week, World Congress of Nephrology (WCN), Southwest Nephrology Congress.
- The following clinical trial registries were searched: ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and European Clinical Trials Register (EU CTR).
- No study design filters or date or language limits were applied to the majority of the searches, although the additional searches conducted on 9 October were limited to RCTs only.
- All database strategies searched for a range of terms for C3G and primary IC-MPGN. The population facet was then combined with a facet which included search terms for pegcetacoplan and a number of comparator treatments. When this limited rather than full list of comparators was queried, in response to clarification the company stated that:

At the time the original SLR was originally conducted, the comparators focused on treatments targeting the complement cascade, in particular C3 modulators which were developed for patients with C3G and IC-MPGN. At the time of the search, iptacoplan in particular was

considered the main comparator. To address this clarification question, and identify any additional studies, an additional search was undertaken (in Embase, MEDLINE and Cochrane on 9 October 2025) which included terms for the original intervention and comparators of interest (pegcetacoplan, iptacopan, ARO-C3, SAR443809, BCX10013, ADX-097, KP104, NM8074 or zaltenibart) as well as terms for standard-of-care treatments as listed in the decision problem Table (angiotensin converting enzyme inhibitors, angiotensin II receptor agonists, corticosteroids, mycophenolate mofetil and sodium-glucose co-transporter-2 inhibitors, other immunomodulatory treatments, eculizumab, etc.). Due to time constraints, the searches focused on randomised controlled trials (RCTs) which provide the most robust evidence for any treatment.³

The EAG assessed the searches submitted by the company and considered them appropriate for identifying references on the additional comparators.

- The EAG noted that EMTREE indexing terms were used in the MEDLINE and Cochrane Library search strategies, rather than the MeSH equivalent. Although mapping between indexing terms does take place, it is good practice to use the database-appropriate subject headings to ensure no potentially relevant records are missed.
- The update searches were conducted by applying a 2024 publication year limit to the original searches. The EAG believed that the use of additional database fields (such as record entry date or update date) would have increased the chance of retrieving records with a pre-2024 publication date which had been added to the database since the date of the original search. Given the small number of records, a simpler and more reliable approach would have been to re-run the searches in their entirety and deduplicate the results against those already found.
- Overall, the clinical effectiveness searches were well structured, transparent and reproducible, and contained a good range of search terms, synonyms and subject headings.

3.1.2 Inclusion criteria

An SLR was conducted to identify all relevant clinical trial evidence associated with the decision problem. Table 3.1 reflects the eligibility criteria used to identify relevant studies.

Table 3.1: Eligibility criteria used in SLR

	Inclusion	Exclusion
Population	• Patients (any age) with primary C3G, including DDD and C3GN • Patients (any age) with primary or idiopathic IC-MPGN	• Patients with secondary C3G/IC-MPGN
Interventions	• Pegcetacoplan (Aspaveli, Empaveli, Syfovre, APL-2)	None listed
Comparators	• Iptacopan (Fabhalta, LNP023) • ARO-C3 • SAR443809 • BCX10013 • ADX-097 • KP104 • NM8074 • Zaltenibart (OMS906)	None listed

	Inclusion	Exclusion
Outcomes	Efficacy, including but not limited to proportion of patients, time to or change in the following: • proteinuria or uPCR (inc. change according to cut off) • eGFR • serum creatinine levels • composite renal outcomes • activity score of C3G histologic index • C3c staining • remission • survival • progressing to ESKD or kidney transplantation and time to progression • mortality/death Safety and tolerability, including but not limited to: • any grade 3/4 AEs • any SAEs • discontinuation due to AEs • AESI Any HRQoL or PRO outcomes (e.g., reported from EQ-5D, SF-36, FACIT-fatigue, KDQOL, PGCI scale)	• Outcomes not relating to economic evaluations, resource use and utilities • PK/PD outcomes
Study design	• RCTs • Interventional non-RCTs: - o non-randomised comparative studies - o single-arm clinical trials - o other prospective, interventional studies, including single arm trials	• Observational, RWE studies • Case reports, case series • Systematic and narrative reviews
Publication type	• Full text publications • Congress abstracts	None listed
Language restrictions	No limits	N/A
Country restrictions	None	N/A
Date restrictions	None	N/A
Adapted from Table 109, CS appendix B⁶ AE = adverse event; AESI = adverse events of special interest; C3G = complement 3 glomerulopathy; C3GN = C3 glomerulonephritis; CS = company submission; DDD = dense deposit disease; eGFR = estimated glomerular filtration rate; EQ-5D = European Quality of Life-5 Dimensions; ESKD = end stage kidney disease; FACIT = Functional Assessment of Chronic Illness Therapy; HRQoL = health-related quality of life; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; KDQOL = Kidney Disease Quality		

	Inclusion	Exclusion
of Life Instrument; N/A = not applicable; PD = pharmacodynamics; PGCI = Patient Global Impression of Change; PK = pharmacokinetics; PRO = patient-reported outcome; RCT = randomised controlled trial; RWE = real-world evidence; SAE = severe adverse event; SF-36 = 36-item Short-form Health Survey; SLR = systematic literature review; uPCR, urinary protein to creatinine ratio		

3.1.3 Critique of screening and data extraction

The company states that two reviewers worked independently to screen records and extract data, with any disagreements or discrepancies resolved through discussion and agreement between the reviewers.⁶ Screening was conducted in two stages. At the first-pass stage, all abstracts and titles identified were screened according to the predefined selection (PICOS) criteria (see Table 3.1). All records selected were then screened at second-pass (full-text stage) by the same two reviewers. The full texts of studies meeting inclusion criteria at this stage were included in the review and progressed to data extraction, critical appraisal and ITC feasibility assessment.

The company do not confirm how data extraction was conducted, and as such the EAG must consider that there is an increased likelihood of error and bias. Had the data extraction been conducted as the screening had with duplicate extractions and disagreements resolved by discussion then this would constitute a reliable and robust method reasonable to minimise errors and biases.

EAG comment: Screening and data extraction were conducted with appropriate methods for reducing error and bias.

3.1.4 Quality assessment

The company do not describe the process by which quality appraisals were conducted. As with data extraction, the company have not provided any information on how many reviewers were involved, whether there were duplicate appraisals conducted independently, or if not, whether appraisals were checked by a second reviewer for accuracy and consistency.

For the original and updated SLR, seven studies met the inclusion criteria and were assessed for risk of bias (RoB). Assessment was carried out using the Cochrane RoB tool for RCTs and the Risk Of Bias In Non-Randomised Studies – of Interventions (ROBINS-I) tool for non-randomised studies. The results of the VALIANT, VALE, NOBLE and DISCOVERY trials were presented in the CS¹ and its appendices.⁷ The EAG has reviewed these appraisals.

Table 3.2: Quality assessment results for VALIANT

VALIANT	Company appraisal	EAG comment if different
Was randomisation carried out appropriately?	Yes	N/A
Was the concealment of treatment allocation adequate?	Yes	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Differences did exist in baseline characteristics at the 5% level. The EAG highlights that this may not reflect any clinical significance but should be

VALIANT	Company appraisal	EAG comment if different
		highlighted and considered when interpreting results.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	N/A
Were there any unexpected imbalances in dropouts between groups?	No	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	N/A
Adapted from Table 18, CS ¹ CS = company submission; EAG = External Assessment Group; N/A = not applicable		

Table 3.3: Quality assessment results for VALE

VALE	Company appraisal	EAG comment if different
Was the cohort recruited in an acceptable way?	Yes	N/A
Was the exposure accurately measured to minimise bias?	Yes	N/A
Was the outcome accurately measured to minimise bias?	Yes	N/A
Have the authors identified all important confounding factors?	Yes	N/A
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	N/A
Was the follow up of patients complete?	N/A, trial is ongoing	N/A
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	N/A
Adapted from Table 19, CS ¹ CS = company submission; EAG = External Assessment Group; N/A = not applicable		

Table 3.4: Quality assessment results for NOBLE

NOBLE	Company appraisal	EAG comment if different
Was randomisation carried out appropriately?	Some concerns	N/A
Was the concealment of treatment allocation adequate?	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Differences did exist in baseline characteristics at the 5% level. The EAG highlights that this

NOBLE	Company appraisal	EAG comment if different
		may not reflect any clinical significance, particularly given small sample sizes, but should be highlighted and considered when interpreting results.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No. The study was not blinded	N/A
Were there any unexpected imbalances in dropouts between groups?	No	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	N/A
Adapted from Table 137, appendix J, CS ⁷ CS = company submission; EAG = External Assessment Group; N/A = not applicable		

Table 3.5: Quality assessment results for DISCOVERY

DISCOVERY	Company appraisal	EAG comment if different
Was the cohort recruited in an acceptable way?	Yes	N/A
Was the exposure accurately measured to minimise bias?	Yes	N/A
Was the outcome accurately measured to minimise bias?	Yes	N/A
Have the authors identified all important confounding factors?	Yes	N/A
Have the authors taken account of the confounding factors in the design and/or analysis?	No, some concerns	N/A
Was the follow up of patients complete?	Yes	N/A
How precise (for example, in terms of confidence interval and p values) are the results?	N/A, Due to the exploratory nature of the study, no formal statistical hypothesis testing was performed.	N/A
Adapted from Table 138, appendix j, CS ⁷ CS = company submission; EAG = External Assessment Group; N/A = not applicable		

EAG comment: The company have not adequately described their methods for appraising these studies. It is important that appraisals are conducted in duplicate or checked by a second reviewer to minimise risks of error and bias. The company should be reminded of the importance of clear reporting

in submissions. Nevertheless, there is no major disagreement with the results of their appraisals although we do comment on baseline differences where relevant.

3.1.5 Evidence synthesis

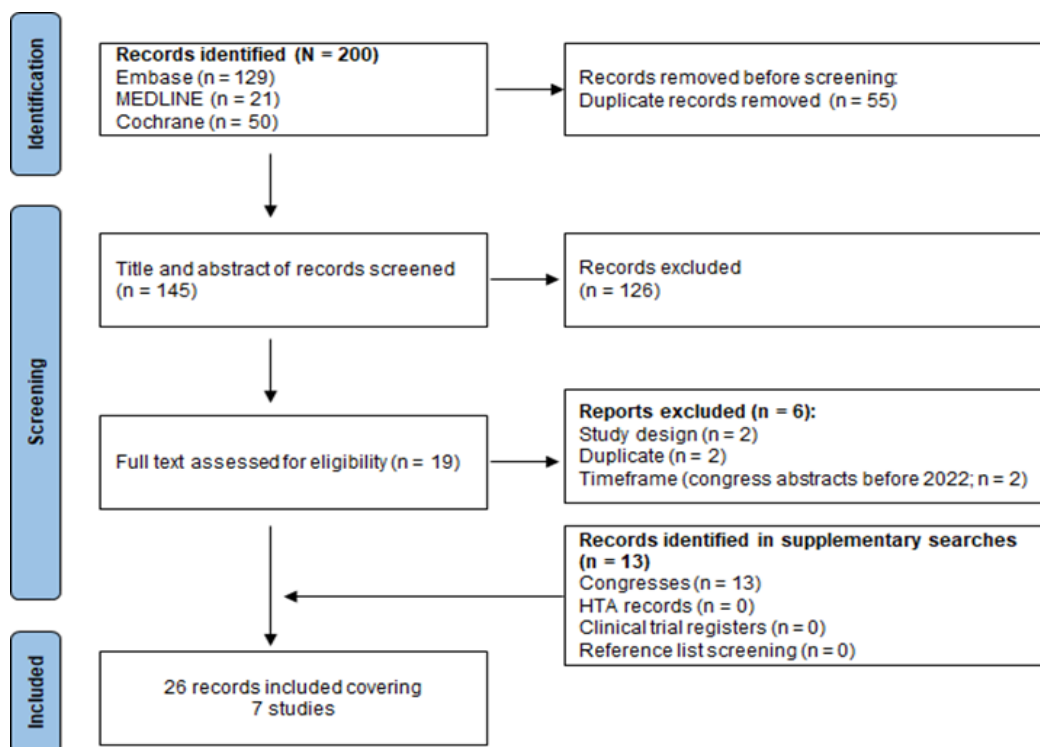
An ITC was conducted to assess the relative efficacy between pegcetacoplan and relevant comparators. Details and the EAG's comments are provided in Sections 3.3 and 3.4 for the ITC.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

An SLR was conducted to identify all relevant clinical trial evidence. Across both the original SLR and subsequent updated searches, 145 articles were screened for inclusion after removal of duplicates. 132 articles were excluded after both stages of screening. Thirteen relevant congress abstracts were identified from supplementary searches. Twenty-six articles, ultimately reporting on seven studies, were deemed to be eligible and were included in this SLR.⁶ The PRISMA flowchart below summarised the process of evidence identification.

Figure 3.1: PRISMA flowchart



Adapted from figure 25, appendix B⁶

HTA = health technology assessment

3.2.2 Summary of included evidence

This section provides a summarised overview of the included evidence as presented and described in the CS.¹

3.2.2.1 *VALIANT trial*

The VALIANT study is a pivotal phase 3, randomised, placebo-controlled, double-blinded, multicentre study to evaluate the efficacy and safety of twice-weekly SC infusions of pegcetacoplan in patients diagnosed with C3G or primary IC-MPGN.¹

The trial started in November 2021 and the first participant in the trial was enrolled on 30 May 2022. The last participant completed on 14 January 2025. The latest data cutoff was 12 February 2025.¹

The planned duration of participation in the study for each participant was a maximum of approximately 70 weeks. The study consisted of four parts:¹

- Part 1: 10-week screening period
- Part 2: 26-week randomised controlled period (RCP)
- Part 3: 26-week open-label period (OLP)
- Part 4: 8-week follow-up period (only for participants who do not roll into a long-term extension study).

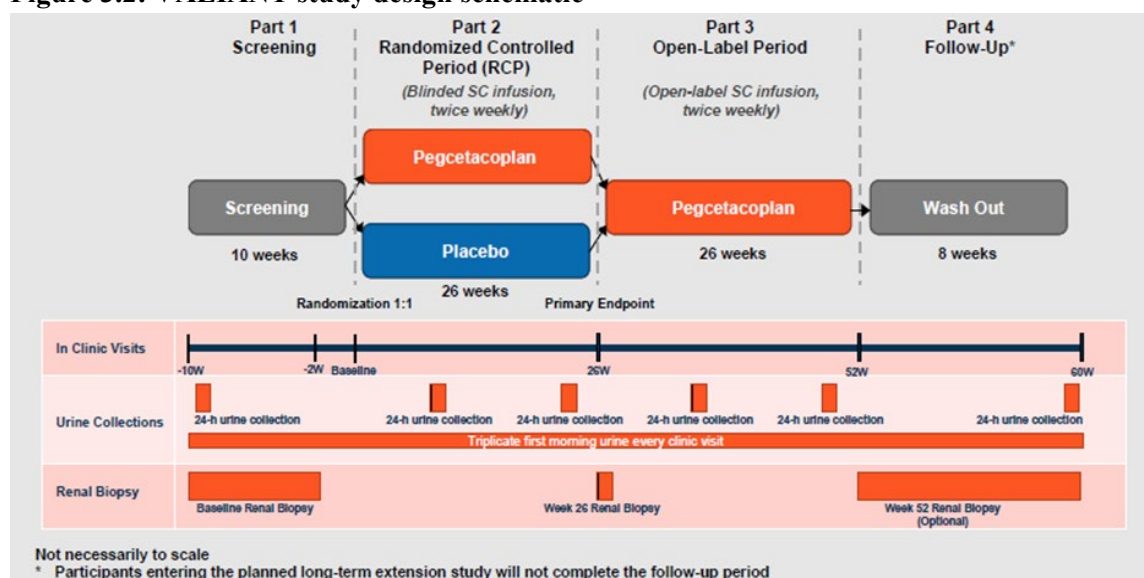
Participants were randomly assigned 1:1, via a computer-generated randomisation schedule, to either the pegcetacoplan group (pegcetacoplan treatment throughout the RCP and OLP) or the placebo group (placebo treatment during the RCP and pegcetacoplan treatment during the OLP).

Stratification factors were applied to the randomisation: (1) participants with post-transplant recurrence versus non-transplant participants and (2) participants with baseline renal biopsies (either collected during screening or a historic biopsy collected within 28 weeks prior to randomisation) versus participants without baseline renal biopsies.¹

At the end of the RCP, a renal biopsy was required for participants aged 18 years and older to advance to the OLP. This was not required for participants younger than 18 years who could have advanced to the OLP upon completion of all assessments for weeks 24 through 26, other than the renal biopsy.

At the end of the RCP, participants from both groups proceeded to the 26-week OLP, in which all participants were treated with pegcetacoplan twice weekly. Open-label dosing began at the first visit after the week 26 renal biopsy for adults and any adolescents providing renal biopsies. Open-label dosing for adolescents not providing renal biopsies started at the week 26 visit. At the end of the OLP, there was an optional renal biopsy. Participants younger than 18 years who did not have a baseline biopsy within 28 weeks of day 1 did not have a biopsy at the end of the OLP. Upon completion of the OLP, participants entered the 8-week follow-up period (part 4) unless they entered a long-term extension study (Study APL2-C3G-314/VALE/ NCT05809531). An estimated 100 participants (of the 120 enrolled in VALIANT), who in the opinion of the investigator had experienced clinical benefit from pegcetacoplan, were invited to participate in the long-term extension study (APL2-C3G-314/VALE).¹

Figure 3.2 and Table 3.6 provide an overview of the trial design and characteristics.

Figure 3.2: VALIANT study design schematicBased on Figure 5, CS¹

CS = company submission; SC = subcutaneous; W = week

Table 3.6: Overview of the pivotal VALIANT trial

Study	VALIANT (NCT05809531)
Study design	Phase 3, randomised, placebo-controlled, double-blinded efficacy and safety trial
Population	C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN)
Intervention(s)	Pegcetacoplan was administered subcutaneously b.i.w. Adults of any weight and adolescents weighing $\geq 50\text{kg}$: 1,080 mg (20 mL) Adolescents weighing 35 to $<50\text{kg}$, 1st dose is 648 mg (12 mL), 2nd dose is 810 mg (15 mL), and maintenance dose is 810 mg (15 mL): Adolescents weighing 30 to $<35\text{kg}$, 1st and 2nd doses are 540 mg (10 mL) and maintenance dose is 648 mg (12 mL).
Comparator(s)	Placebo (matching volumes)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	Proteinuria reduction; stabilisation of deterioration in eGFR; mortality; adverse effect of treatment; HRQoL
All other reported outcomes	Reduction in C3c staining C3G histologic activity score index

Adapted from Table 4, CS¹
b.i.w. = twice weekly; C3G = complement 3 glomerulopathy; CS = company submission; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; N/A = not applicable

VALIANT was conducted in 122 sites across 19 countries including the following: Argentina (3 sites), Australia (4 sites), Austria (2 sites), Belgium (4 sites), Brazil (14 sites), Canada (2 sites), Czechia (2 sites), France (11 sites), Germany (6 sites), Israel (2 sites), Italy (10 sites), Japan (8 sites), Netherlands (3 sites), Poland (2 sites), South Korea (4 sites), Spain (8 sites), Switzerland (3 sites), UK (9 sites), and US (25 sites).¹

Eligibility criteria for participation in the study are detailed in Table 3.7.

Table 3.7: Key eligibility criteria for VALIANT

Inclusion	Exclusion
Aged at least 18 years; where approved, adolescents (aged 12-17 years) weighing at least 30 kg may also be enrolled.	Previous exposure to pegcetacoplan.
A diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant)	Evidence of improving renal disease in the 8 weeks prior to screening or during the screening period according to available data; improving renal disease is defined as >30% increase in eGFR or >50% decrease in proteinuria.
Evidence of active renal disease, based on one or more of the following: 1. In adults or adolescents with a baseline renal biopsy (either one collected during screening or a historic biopsy collected within 28 weeks prior to randomisation), at least 2+ C3c staining on the baseline renal biopsy 2. In adolescents not providing a baseline renal biopsy, at least one of the following: • Plasma sC5b-9 level above the upper limit of normal during screening • Serum C3 below the lower limit of normal (LLN) during screening • Presence of an active urine sediment during screening, as evidenced by haematuria with at least 5 red blood cells per high-power field and/or red blood cell casts on routine local or central microscopic analysis of urine • Presence of C3 nephritic factor within 6 months of screening, based on central laboratory results or medical history	From a renal transplant participant, evidence of rejection that requires treatment in the baseline renal biopsy collected during screening.
No more than 50% global glomerulosclerosis or interstitial fibrosis on the baseline biopsy for adult participants or adolescent participants providing a baseline biopsy	C3G/IC-MPGN secondary to another condition (e.g., infection, malignancy, monoclonal gammopathy, a systemic autoimmune disease such as systemic lupus erythematosus, chronic antibody-mediated rejection, or a medication), in the opinion of the investigator
At least 1 g/day of proteinuria on a screening 24-hour urine collection and a uPCR of at least 1000 mg/g in at least 2 FMU samples collected during screening	Current or prior diagnosis of HIV, hepatitis B, or hepatitis C infection or positive serology during screening that is indicative of infection with any of these viruses

Inclusion	Exclusion
eGFR ≥ 30 mL/min/1.73 m ² calculated by the CKD-EPI creatinine equation for adults or the Bedside Schwartz equation for adolescents	Body weight greater than 100 kg at screening.
Stable regimen for C3G/IC-MPGN treatment, as described below: Angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and/or sodium-glucose cotransporter-2 inhibitor (SGLT2) therapy that is stable and optimised, in the opinion of the investigator, for at least 12 weeks prior to randomisation Stable doses of other medications that can affect proteinuria (e.g., steroids, mycophenolate mofetil, and/or other allowed immunosuppressants that the participant is receiving for treatment of C3G or IC-MPGN) for at least 12 weeks prior to randomisation If a participant is on prednisone (or other systemic corticosteroid) for C3G or IC-MPGN treatment, the dosage is stable and no higher than 20 mg/day (or equivalent dosage of a corticosteroid other than prednisone) for at least 12 weeks prior to randomisation	Hypersensitivity to pegcetacoplan or to any of the excipients.
Have received vaccinations against <i>S pneumoniae</i> , <i>N meningitidis</i> (types A, C, W, Y, and B), and H influenzae (type B) as per ACIP recommendations for adults or children with complement deficiencies. Vaccination series should be initiated at least 14 days prior to randomisation. Vaccination is mandatory unless documented evidence exists that participants are non-responders to vaccination	History of meningococcal disease.
	Malignancy, except for the following: Cured basal or squamous cell skin cancer Curatively treated in situ disease Malignancy-free and off treatment for ≥ 5 years.
	Severe infection (e.g., requiring IV antibiotic therapy) within 14 days prior to the first dose of pegcetacoplan.
	An absolute neutrophil count $< 1,000$ cells/mm ³ at screening.
	Significant other renal disease that would, in the opinion of the investigator, confound interpretation of study results.
	Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or 5 half-lives from the last dose of investigational agent (whichever is longer) prior to screening period.

Inclusion	Exclusion
	Use of rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan within 5 half-lives of that product prior to the screening period.
Adapted from Table 7 of the CS ¹ ACEi = angiotensin-converting enzyme inhibitor; ACIP = Advisory Committee on Immunization Practices; ARB = angiotensin receptor blocker; C3G = complement 3 glomerulopathy; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CS = company submission; eGFR = estimated glomerular filtration rate; FMU = first morning urine; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IV = intravenous; LLN = lower limit of normal; SGLT2 = sodium-glucose cotransporter-2; uPCR = urinary protein to creatinine ratio	

All participants received SC infusions of pegcetacoplan or matching volumes of placebo twice weekly in addition to any pre-existing SoC.¹ Dosing regimens as presented in the CS are described below in Table 3.8.

Table 3.8: Dosing regimens for VALIANT

Weight	First dose (infusion volume)	Second dose (infusion volume)	Maintenance dosing regimen (infusion volume)
All adult participants, adolescent participants ≥ 50 kg	1,080 mg (20 mL)	1,080 mg (20 mL)	1,080 mg twice weekly (20 mL)
Adolescent participants 35 to <50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
Adolescent participants 30 to <35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)
Adapted from Table 8, CS ¹ If a participant missed any regularly scheduled doses for any reason, all efforts were made to restart dosing as soon as possible to reach and maintain therapeutic steady-state concentrations of pegcetacoplan CS = company submission			

Dosing was blinded in the RCP; the OLP was not blinded. All central evaluations were blinded to treatment assignment. Participants, the sponsor, investigators, and all study site personnel conducting study-related activities (including carrying out study procedures, evaluating participants, and entering and/or evaluating study data) remained blinded to treatment allocations during the RCP at least until all participants had completed the week 26 assessments and the RCP portion of the database had been locked. Although treatment in the OLP was not blinded, investigators, study site personnel, and participants remained blinded to the RCP treatment assignment.¹

Concomitant medications included angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and/or sodium-glucose cotransporter-2 (SGLT2) inhibitors. Additionally, other medications that could affect proteinuria, including steroids, mycophenolate mofetil (MMF), and/or other allowed immunosuppressants that the participant is receiving for treatment of C3G or primary IC-MPGN.¹ Prohibited medications included rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan (including, but not limited to, eculizumab and/or ravulizumab) was prohibited within 5 half-lives of that product prior to screening and for the duration of the study.¹ In the event of an increase in serum creatinine to at least 2 times the baseline level that in the opinion of the investigator was due to the underlying C3G/IC-MPGN disease, rescue therapy could be considered, such as high-dose corticosteroids and/or C5 inhibitor treatment.¹

The primary objective was to assess the efficacy of twice-weekly SC doses of pegcetacoplan compared with that of placebo in patients with primary C3G or IC-MPGN on the basis of a reduction in proteinuria.¹

Secondary objectives included:¹

- The effect of pegcetacoplan on estimated glomerular filtration rate (eGFR)
- The effect of pegcetacoplan on additional C3G/primary IC-MPGN disease-related parameters
- The safety of pegcetacoplan over 52 weeks of treatment.

EAG comment: No clinical effectiveness evidence was presented in the main CS for NOBLE. The company stated that it was not used to populate the economic model due to the small sample size and differences between it and the larger VALIANT trial, which prevented pooling. As discussed in Section 3.3, the EAG agreed with the company's justification.

3.2.2.2 NOBLE trial

NOBLE was a multinational, prospective phase 2 RCT investigating the efficacy and safety of 12 weeks of pegcetacoplan or standard of care in 13 adult patients with recurrent C3G (n = 10) or IC-MPGN after kidney transplant. Patients were enrolled at 23 sites across 11 countries: The US, Netherlands, France, Spain, Italy, Switzerland, Austria, UK, Argentina, Brazil, and Australia. Table 3.9 provides an oversight of the trial characteristics.¹

Table 3.9: NOBLE details

Study	NOBLE (NCT04572854)
Study design	Phase 2, open-label, randomised, controlled efficacy and safety trial
Population	Adult patients with post-transplant recurrence of C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN)
Intervention(s)	1,080 mg of pegcetacoplan was administered subcutaneously twice weekly for the duration of the main study period from weeks 1 to 52. Biopsies occurred on weeks 12 and 52.
Comparator(s)	No treatment with pegcetacoplan was given during the randomised controlled portion of the study (Weeks 1 to 12). After week 12, subjects received 1,080mg of pegcetacoplan subcutaneously twice weekly for the remainder of the trial until week 52. Biopsies occurred on week 52.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale if study not used in model	The trial had a small sample size and short duration of randomised controlled trial period (12 weeks); therefore, results are less appropriate for inclusion than the VALIANT data. In addition, there were differing inclusion criteria in terms of eGFR levels and age requirements, meaning it may not be appropriate to pool the outcome data with that collected in VALIANT.
Reported outcomes specified in the decision problem	Stabilisation or changes in eGFR Changes in proteinuria

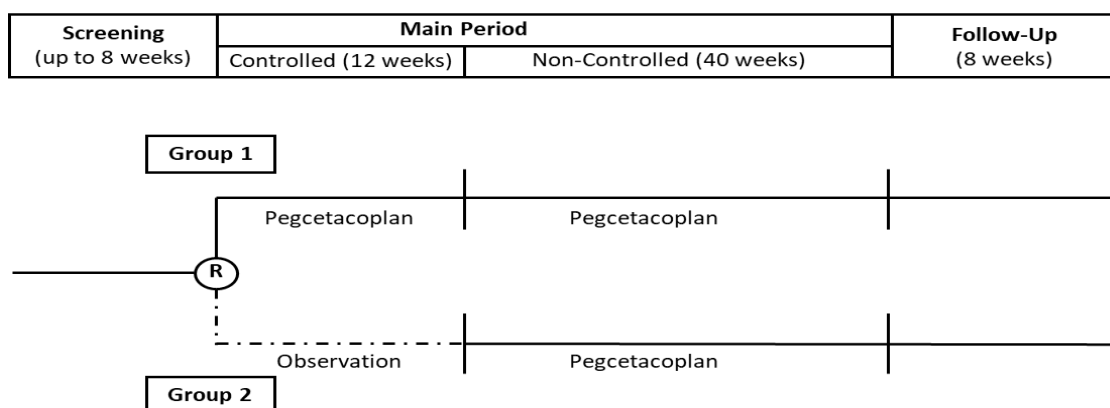
Study	NOBLE (NCT04572854)
	Adverse effect of treatment
All other reported outcomes	Changes in C3c staining over time. Stabilisation or changes in serum creatinine concentration
Adapted from Table 5, CS ¹ C3G = complement 3 glomerulopathy; CS = company submission; eGFR = estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis	

The planned duration of the overall participation in the core study (part A) was a maximum of approximately 68 weeks which consisted of:⁷

- An 8-week screening period
- Part A: 52-week main study period
- An 8-week follow-up period
- Part B: long-term extension that could extend until pegcetacoplan is commercially available for the studied indication.

During the screening period, a renal allograft biopsy occurred. The main study period consisted of two parts: a controlled period from weeks 1–12 and a non-controlled portion from weeks 13–52. The study design for part A is summarised in Figure 3.3 below.

Figure 3.3: NOBLE Study design (Part A)



Adapted from figure 47, CS appendix J⁷

CS = company submission; R = randomisation

During the main period, patients were randomised in a 3:1 ratio to Group 1 or Group 2. Participants in group 1 received their initial doses of pegcetacoplan on day 1 and continued to receive pegcetacoplan on the first and fourth days (day 1 and day 4) of each treatment week until week 52. Those in group 2 received their initial doses of pegcetacoplan after the week 12 renal biopsy. Then, the participants continued to receive pegcetacoplan on the first and fourth days of each treatment week until week 52.⁷ Any participant who was experiencing clinical benefit (determined by investigator) from pegcetacoplan administration could participate in part B, a long-term extension, to continue receiving pegcetacoplan until it is commercially available for the disease under study. Participants could enter part B immediately following the 52-week treatment period and did not have to complete the 8-week follow-up period.⁷ Treatment consisted of 1,080 mg of pegcetacoplan given subcutaneously twice weekly, and dosing remained consistent throughout the duration of the 52 weeks, follow-up period and long-term extension.

The eligibility criteria for NOBLE are detailed below.

Table 3.10: NOBLE eligibility criteria

Inclusion	Exclusion
Aged at least 18 years	Absolute neutrophil count <1,000 cells/mm ³ during screening (not including day 1)
Clinical and pathologic evidence of recurrent C3G or IC-MPGN, as evidenced by all of the following: • A diagnosis of C3G or IC-MPGN, with at least 2+ staining for C3c in the renal allograft, confirmed by a central pathologist, based on the screening renal allograft biopsy • C3G or IC-MPGN must be primary and not secondary to another condition (e.g., infection, malignancy, monoclonal gammopathy, autoimmunity, chronic antibody-mediated rejection, chronic thrombotic microangiopathy, or a medication)	Previous treatment with pegcetacoplan.
Stable (not improving) or worsening disease, in the opinion of the investigator, in the 2 months preceding the first dose of pegcetacoplan.	Evidence of rejection on the screening renal allograft biopsy that requires treatment.
eGFR ≥ 15 mL/min/1.73 m ² , calculated by the CKD-EPI creatinine equation for adults.	Diagnosis or history of HIV, hepatitis B, or hepatitis C infection or positive serology at screening indicative of infection with any of these viruses.
No more than 50% glomerulosclerosis or interstitial fibrosis on the screening renal biopsy.	Weighed more than 100 kg at screening.
Stable regimen for recurrent C3G/IC-MPGN for at least 4 weeks prior to the screening renal allograft biopsy and from the time of the screening renal allograft biopsy until randomisation.	Hypersensitivity to pegcetacoplan or to any of the excipients.
Had received required vaccinations against N. meningitidis, S. pneumoniae, and H. influenzae (type B) or agreed to receive vaccinations if applicable vaccination records were not available. Vaccination was mandatory unless documented evidence existed that participants were non-responders to vaccination.	History of meningococcal disease.
Women of childbearing potential, defined as any women who had experienced menarche and who were not permanently sterile or postmenopausal, were required to have a negative blood pregnancy test at screening (and negative urine pregnancy at visit 4) and agree to use protocol-defined methods of contraception from screening through 12 weeks after receiving last dose of pegcetacoplan.	Malignancy, except for the following: Cured basal or squamous cell skin cancer Curatively treated in situ disease Malignancy free and off treatment for ≥ 5 years
Men were required to agree to use protocol-defined methods of contraception and agree to refrain from donating semen from screening	Significant renal disease in the renal allograft secondary to another condition (e.g., infection, malignancy, monoclonal gammopathy, rejection, or a medication) that

Inclusion	Exclusion
through 12 weeks after receiving last dose of pegcetacoplan.	would, in the opinion of the investigator, confound interpretation of the study results.
Willing and able to provide written informed consent.	Participation in any other investigational drug study or exposure to other investigational agent, device, or procedure within 30 days or 5 half-lives from the last dose of the investigational agent (whichever is longer) prior to screening period.
Able to understand and willing to comply with all scheduled procedures and other requirements of the study in the opinion of the investigator.	Women who were pregnant or who were breastfeeding.
Willing and able to self-administer pegcetacoplan or have an identified caregiver who can perform the administration.	Inability to cooperate or any condition that, in the opinion of the investigator, could increase the participant's risk by participating in the study or confound the outcome of the study.
	Evidence of drug or alcohol abuse or dependence, in the opinion of the investigator.
	Known or suspected hereditary fructose intolerance.
Adapted from Table 129 of the CS ⁷ C3G = C3 glomerulopathy; CKD-EPI = Chronic Kidney Disease–Epidemiology Collaboration; CS = company submission; eGFR = estimated glomerular filtration rate; H. influenzae = Haemophilus influenzae; HIV = human immunodeficiency virus; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; N. meningitidis = Neisseria meningitidis; S. pneumoniae = Streptococcus pneumoniae	

Medications administered and procedures performed from informed consent through to the end-of-study visit were regarded as concomitant and were documented. Participants were recommended to be on stable doses of all medications relevant to their renal disease for at least 4 weeks prior to the screening renal allograft biopsy until the end of the study. Use of rituximab, belimumab, eculizumab, and ravulizumab during the study (and/or within 24 weeks prior to the first dose of pegcetacoplan) was required to be discussed with the sponsor for consideration and approval. In the setting of an acute crescentic glomerulonephritis at the time of study entry, steroid treatment could be initiated along with or around the same time as pegcetacoplan treatment if deemed necessary by the investigator.⁷

The primary objective was to evaluate the efficacy of pegcetacoplan in improving the underlying pathophysiology of C3G/ IC-MPGN after 12 weeks of treatment.

Secondary objectives included:

- The effect of pegcetacoplan on key clinical manifestations of the disease after 52 weeks of treatment.
- The safety of pegcetacoplan for up to 52 weeks in participants with recurrent C3G/IC-MPGN in a renal allograft.

3.2.2.3 *DISCOVERY trial*

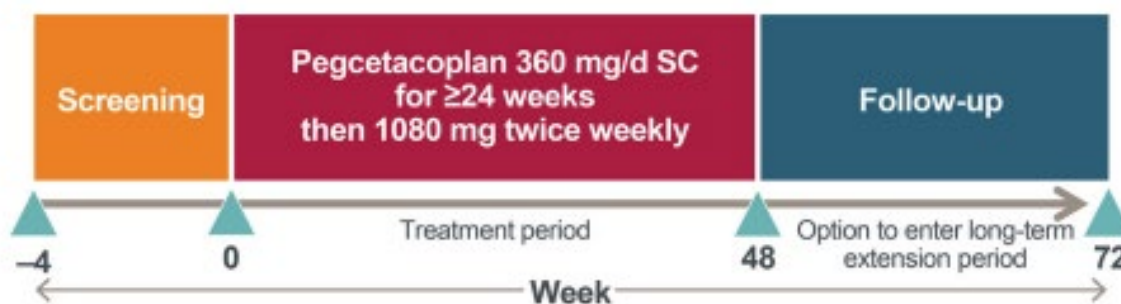
DISCOVERY is a US based single-arm, open-label, phase 2 study to evaluate preliminary efficacy and safety outcomes with the use of pegcetacoplan in patients with complement-mediated glomerulopathies.⁷

The study consisted of three parts:

- Part 1: 4-week screening period
- Part 2: 26-week main treatment period
- Part 3: 25-week follow period.

Following part 2, patients who were experiencing clinical benefit from pegcetacoplan were invited to participate in a long-term extension phase to continue to receive treatment with pegcetacoplan until commercially available for the disease under treatment.⁷ An overview of the trial is provided below in Figure 3.4. Treatment consisted of 360 mg of pegcetacoplan given subcutaneously daily through at least week 24, after which patients could transition to a dosing regimen of 1,080 mg twice weekly⁷.

Figure 3.4: DISCOVERY Study design



Adapted from figure 48, CS appendix J⁷

CS = company submission; SC = subcutaneous

The eligibility criteria for participation in DISCOVERY are detailed in Table 3.11.

Table 3.11: DISCOVERY eligibility criteria

Inclusion	Exclusion
Aged at least 16 years at screening	Patients with kidney disease secondary to another condition (e.g., infection, malignancy, monoclonal gammopathy, and medication).
Diagnosis of C3G confirmed by low C3 level or historical kidney biopsy; presence of proteinuria, defined as a 24-hour uPCR >750 mg/g; eGFR ≥30 ml/min per 1.73 m ² .	
Stable or worsening kidney disease while on stable and optimised treatment for ≥2 months before the first dose of pegcetacoplan.	
Received the required vaccinations against encapsulated bacteria, including <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i> , and <i>Haemophilus influenzae</i> type B at least 2 weeks prior to the first dose of pegcetacoplan.	
Adapted from Table 130, CS appendix J ⁷ C3G = C3 glomerulopathy; CS = company submission; eGFR = estimated glomerular filtration rate; uPCR = urinary protein to creatinine ratio	

Patients were expected to be on a stable and optimised treatment regimen for their disease, in the opinion of the investigator, for at least 2 months before the first dose of pegcetacoplan; therapies included, but were not limited to, antihypertensive, antiproteinuric, and immunosuppressive agents.⁷

The primary objective was to assess the change in proteinuria from baseline to week 48, measured by 24-hour uPCR.

Secondary objectives:

- Complete clinical remission, defined as normalisation of proteinuria (<200 mg/g) at week 48
- Stabilisation or improvement in eGFR from baseline to week 48
- Changes in serum and plasma disease biomarkers.

EAG comment: This trial is not considered any further due to the existence of RCT data in the form of VALIANT, and longer-term follow-up data on pegcetacoplan in the form of VALE.

3.2.2.4 VALE trial

VALE is a phase 3, open-label, single arm, multicentre study conducted over 44 sites across 15 countries including: Argentina (1 site), Australia (2 sites), Belgium (1 site), Brazil (8 sites), Czechia (1 site), France (2 sites), Israel (1 site), Italy (3 sites), Japan (2 sites), Netherlands (3 sites), South Korea (3 sites), Spain (3 sites), Switzerland (1 site), UK (2 sites), and US (11 sites).¹ The aim was to evaluate the long-term safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients with C3G or primary IC-MPGN. It is open to those patients who have completed participation in study NCT05809531/VALIANT and had experienced clinical benefit from pegcetacoplan administration.¹ The latest data cutoff was 20 June 2024. The trial is ongoing. At 20 June 2024, 53 participants were enrolled.¹

Participation is for a minimum of 120 weeks and patients may continue to receive treatment with pegcetacoplan until it is commercially available for treatment, or the development programme is terminated. Participants can enter this study as soon as their 52-week treatment period in VALIANT has ended; completion of the 8-week follow-up period described in the VALIANT protocol is not required. Participants will be evaluated every 12 weeks for the duration of this study. Safety and efficacy will be monitored at each visit.¹

Following completion of the study, participants started follow-up phase or completed a transition visit, depending on whether they would continue to receive pegcetacoplan. Participants who discontinued pegcetacoplan entered the follow-up and returned for an exit visit 8 weeks after their last dose. Those who transitioned to commercially available or alternately sourced pegcetacoplan completed the transition visit. Participants were to complete either the follow-up period or the transition visit, but not both.¹

The eligibility criteria for the VALE trial are described below in Table 3.12

Table 3.12: VALE eligibility criteria

Inclusion	Exclusion
Participants must have completed participation in Study APL2-C3G-310/VALIANT through the week 52 visit requirements.	Any condition that, in the opinion of the investigator, creates an undue risk for the participant by participating in the study or is likely to confound interpretation of the study results.

Inclusion	Exclusion
Participants must have experienced clinical benefit from pegcetacoplan while participating in the previous study, in the opinion of the investigator.	Female participants who are or are planning to become pregnant or who are currently breastfeeding and are unwilling to discontinue for the duration of the study and for at least 90 days after the final dose of study drug.
Participants must remain on a stable regimen for C3G or primary IC-MPGN treatment according to the requirements of VALIANT.	Any condition that, in the opinion of the investigator, creates an undue risk for the participant by participating in the study or is likely to confound interpretation of the study results.
Participants must have received vaccinations against <i>S. pneumoniae</i> , <i>N. meningitidis</i> (types A, C, W, Y, and B), and <i>H. influenzae</i> (type B) according to the requirements of the VALIANT study and agree to receive any additional vaccinations recommended according to ACIP recommendations for adults or children with complement deficiencies and/or immunocompromising conditions or other similar local applicable guidelines	
Adapted from Table 9, CS ¹ ACIP = Advisory Committee on Immunization Practices; C3G = C3 glomerulopathy; CS = company submission; <i>H. influenzae</i> = <i>Haemophilus influenzae</i> ; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; <i>N. meningitidis</i> = <i>Neisseria meningitidis</i> ; <i>S. pneumoniae</i> = <i>Streptococcus pneumoniae</i>	

All participants received SC infusions of pegcetacoplan twice weekly, which was the protocol during VALIANT. The dosing regimens for pegcetacoplan in VALE matched the maintenance dosing regimen from VALIANT.

If serum creatinine increased to at least 2 times the baseline level due to the underlying C3G or primary IC-MPGN disease, rescue therapy could be considered, such as high-dose corticosteroids, C5 inhibitor treatment, or both. If rescue therapy was instituted, the participant was considered a non-responder for the analysis of any efficacy endpoints based on the proportion of participants meeting a specified criterion. If a participant received rescue therapy that was not a prohibited concomitant medication, they were allowed to remain on study drug, although that participant was deemed a non-responder for the analysis of any efficacy endpoints based on the proportion of participants meeting a specified criterion. If a participant received rescue therapy that was a prohibited concomitant medication, that participant was discontinued from the study and deemed a non-responder.¹ The use of rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan (including but not limited to eculizumab and/or ravulizumab) was prohibited for the duration of the study.¹

The primary outcome is the proportion of participants with a reduction in proteinuria over time compared to pretreatment.

Secondary outcomes include:¹

- The proportion of participants with eGFR values that are stable or improved from pretreatment values over time

- The proportion of participants with normalisation of serum albumin and serum C3 levels over time
- Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score
- Time to progression to a composite clinical outcome (at least one of the following: sustained doubling of serum creatinine, progression to CKD stage 5 or end-stage renal (ESRD) disease, renal transplantation, or death from renal or cardiovascular disease).

Safety outcomes include:¹

- Treatment emergent adverse events (TEAEs)
- The number and incidence of rejection episodes (for post-transplant participants only)
- The number and incidence of graft loss (for post-transplant participants only)
- The incidence of death, stratified by transplant history and overall.

3.2.3 Statistical analysis

This section provides a brief overview of the statistical methodologies of the relevant trials as they are described and presented in the CS.

3.2.3.1 VALIANT

A total of 124 participants were enrolled (see Table 3.13), including 63 participants in the pegcetacoplan group and 61 participants in the placebo group. 116 (93.5%) participants overall completed the RCP study treatment (pegcetacoplan: 59 [93.7%]; placebo: 57 [93.4%]). The number of participants completing treatment was balanced between arms.⁶

The most common reason for treatment discontinuation was due to an adverse event (AE) (pegcetacoplan: 2 [3.2%]; placebo: 1 [1.6%]). The most common reason for study discontinuation was due to a participant withdrawing consent (pegcetacoplan: [0.0%]; placebo: 2 [3.3%]). There were 2 participants (3.2%) in pegcetacoplan group and 4 participants (6.6%) in placebo group who withdrew from the study. In the pegcetacoplan group, 1 participant was withdrawn from the study due to an investigator or medical monitor decision, while the second participant died because of respiratory failure due to COVID-19 pneumonia; this was reported as not related to pegcetacoplan, according to the investigator and sponsor. One participant in the placebo group withdrew from the study due to pregnancy. Two participants in the placebo group also withdrew consent, and 1 participant was lost to follow-up.⁶

Table 3.13: Participant disposition for RCP (ITT Set)

Characteristics	Pegcetacoplan (N=63) n (%)	Placebo (N=61) n (%)	Overall (N=124) n (%)
Participants treated	63 (100.0)	61 (100.0)	124 (100.0)
Participants ongoing with study treatment ^a	2 (3.2)	0	2 (1.6)
Participants who completed treatment ^b	59 (93.7)	57 (93.4)	116 (93.5)
Participants who discontinued study treatment	2 (3.2)	4 (6.6)	6 (4.8)
Adverse event			
Participants withdrew consent	2 (3.2)	1 (1.6)	3 (2.4)
Pregnancy	0	1 (1.6)	1 (0.8)
Participants noncompliance	0	1 (1.6)	1 (0.8)
	0	1 (1.6)	1 (0.8)

Participants who withdrew from study	2 (3.2)	4 (6.6)	6 (4.8)
Participants withdrew consent	0	2 (3.3)	2 (1.6)
Lost to follow-up	0	1 (1.6)	1 (0.8)
Investigator/medical monitor decision	1 (1.6)	0	1 (0.8)
Pregnancy	0	1 (1.6)	1 (0.8)
Death	1 (1.6)	0	1 (0.8)
Adapted from Table 113, CS ⁶			
^a Participants who had completed week 26 assessment but had not started the OLP by the data cut.			
^b Participants who had completed treatment of the RCP and continued into the OLP.			
CS = company submission; ITT = intention-to-treat; OLP = open-label period; RCP = randomised controlled period			

Table 3.14 summarises the statistical methodology utilised in the VALIANT trial. Randomisation stratification factors were adjusted for analysis of efficacy endpoints in the overall population. These included:¹

- Participants with post-transplant recurrence versus non-transplant participants
- Participants with baseline renal biopsies versus participants without baseline renal biopsies.

If participants were found to have had the incorrect stratum assigned at randomisation, they were analysed according to the randomisation stratum.

There were four analysis populations described within the VALIANT trial. These included the following:¹

- *Screened set*: Included all participants who provide written informed consent. used to describe participant disposition.
- *Intention-to-Treat (ITT) Set*: Included all randomised participants. Participants were to be analysed according to their assigned treatment, regardless of the treatment actually received. All efficacy analyses were performed with the ITT set.
- *Safety Set*: Included all participants who received at least one dose of study drug in the RCP. Participants were analysed according to the treatment they received. All safety analyses were performed with the safety set.
- *Per-Protocol (PP) Set*: Included all participants in the ITT set who had not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Deviations that affect exclusion from the PP set are a subset of protocol deviations; major protocol deviations did not necessarily result in exclusion of the participant from the PP set.

Table 3.14: Summary of VALIANT statistical analyses

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
The primary efficacy endpoint is the log-transformed ratio of uPCR at week 26 compared to baseline. The null ($H_{1,0}$) and alternative ($H_{1,1}$) hypotheses for the primary efficacy analysis are: $H_{1,0}$: There is no difference in log-transformed ratio of uPCR at week 26 compared to baseline between the pegcetacoplan and placebo treatment groups. $H_{1,1}$: There is a difference in log-transformed ratio of uPCR at week 26 compared to baseline between the pegcetacoplan and placebo treatment groups.	Efficacy end points were analysed in the ITT set. The safety set included all patients who received ≥ 1 dose of study treatment. All statistical tests were performed at 2-sided 5% level of significance and all confidence intervals were two-sided 95% confidence intervals. Continuous outcomes were analysed using a mixed-effects model for repeated measures, including fixed categorical effects and fixed covariate of the baseline value of the end point. A logistic regression model (including treatment group as an independent variable and adjusted for baseline value of the variable[s] to define the end point, disease type, and stratification factors) was used to analyse binary outcomes. An analysis of covariance was used to analyse C3G histologic index activity score with treatment as a fixed effect adjusted for baseline	Approximately 80 to 100 participants, including patients with native kidney disease or post-transplant, will be randomised 1:1 to pegcetacoplan or placebo with 40 to 50 participants per arm. Based on preliminary data from Study APL2-201, a reduction of 60% in uPCR in the pegcetacoplan group at week 26 is assumed vs a reduction of 20% in uPCR in the placebo arm, which corresponds to a mean log ratio to baseline of -0.92 vs -0.22 respectively, and a standard deviation of 0.88 (on log-scale). Based on this assumption, a sample size of 70 participants in total provides at least 90% power at 1-sided significance level of 0.025. Considering a 10% attrition to account for potential missing assessments and the impact of coronavirus disease 2019	The primary analysis, including all efficacy and safety end points at 26 weeks, was conducted when all patients completed the week 26 assessment or discontinued. For summary of disposition, the number and percentage of participants who were treated, who were ongoing with study treatment, who completed study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, who completed the study, who withdrew from the study with a primary reason for withdrawal will be summarised and listed using the ITT set.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	score of the end point, disease type, and stratification factors. The data cut-off for this primary analysis (RCP) was 20 June 2024. To preserve the overall type I error among the primary endpoint and key secondary endpoints, the secondary endpoints were analysed using a fixed-sequence hierarchical testing strategy. Hence, the statistical significance of the first secondary endpoint was evaluated only if statistical significance was achieved with the primary analysis of the primary endpoint. Analysis of the remaining key secondary endpoints also adhered to this hierarchical testing strategy.	(COVID-19), it is expected that at least 78 participants with native kidney disease should be enrolled. A minimum of 63 participants with C3G in native kidneys will be enrolled, which is approximately 80% of the enrolled participants with native kidney disease.	
Adapted from Table 17, CS¹ C3G = C3 glomerulopathy; CS = company submission; ITT = intention-to-treat; RCP = randomised controlled period; uPCR = urinary protein to creatinine ratio			

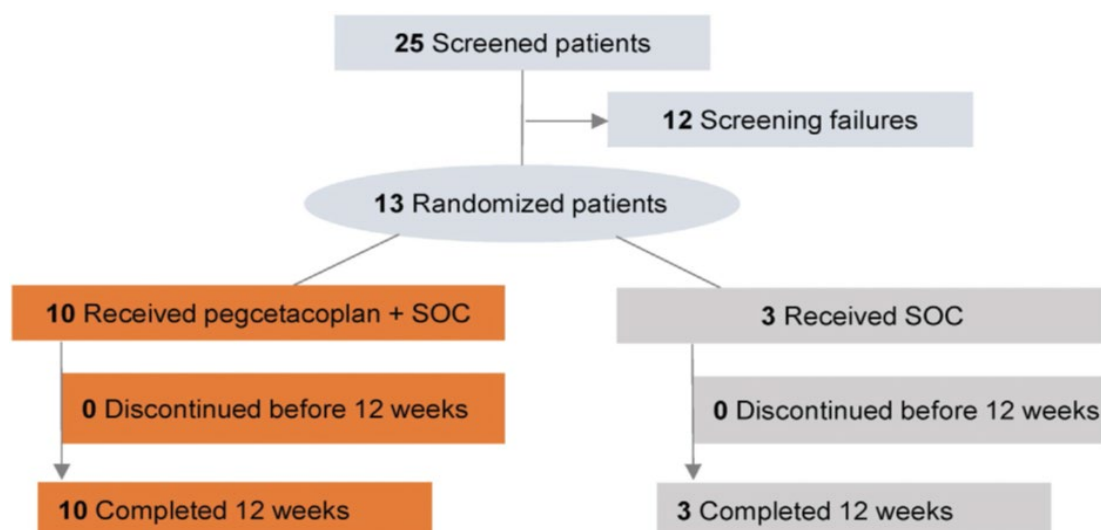
3.2.3.2 NOBLE trial

Three analysis sets were described and are described as follows:⁷

- *Screened sets:* All subjects who provided written informed consent. Used for the summary of analysis sets.
- *Intention-to-Treat Set:* Includes all subjects who were randomised. Used for the summary of demographics, baseline characteristics, subject disposition, and analysis of all efficacy data.
- *Safety set:* Includes all subjects who received at least one dose of pegcetacoplan, and subjects who were randomised into group 2. All safety analyses will be conducted using the safety set.

Twenty-five patients were screened, and 13 participants were enrolled including 10 participants in group 1 (pegcetacoplan-plus-SOC group) and 3 participants in group 2 (SoC-only group) (see Figure 3.5). All participants completed the controlled portion (i.e., the first 12 weeks), and 10 participants (76.9%) (including 8 participants in group 1 and 2 participants in group 2) completed treatment up to week 52. Three participants (23.1%) discontinued and withdrew from the study during the non-controlled portion, including 2 participants (15.4%) due to AEs and 1 participant (7.7%) due to physician decision.⁷

Figure 3.5: Patient disposition



SOC = standard of care

A summary of the statistical methods is presented in the Table 3.15 below.

Table 3.15: Summary of statistical analyses

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
The primary efficacy endpoint is the proportion of participants with a reduction in C3c staining on renal biopsy after 12 weeks of treatment with pegcetacoplan. Due to the exploratory nature of the study, no formal hypothesis testing was performed.	Descriptive statistics were used to summarise continuous variables (e.g., n, mean, first quartile, third quartile, SD, median, minimum and maximum) Due to the exploratory nature of the study, no formal statistical hypothesis testing was performed.	12 planned participants who had post-transplant recurrence of C3G or IC-MPGN. Participants were randomised 3:1 to group 1 (pegcetacoplan treatment throughout the 52-week main period) or group 2 (no pegcetacoplan treatment for the first 12 weeks of the main period, followed by pegcetacoplan treatment).	The analysis of data from the part A controlled portion of the study was performed when all participants had completed the part A controlled portion or discontinued early. The analysis of data from the part A non-controlled portion was performed once all participants had completed the part A non-controlled portion or discontinued early.
Adapted from Table 136 of the CS.¹ C3G = C3 glomerulopathy; CS = company submission; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; SD = standard deviation			

EAG comment: The EAG considers that the statistical analysis approaches used by the company appear to be satisfactory.

3.2.4 Baseline characteristics

3.2.4.1 VALIANT baseline characteristics

The CS provides detailed tabulated data to describe the baseline characteristics of participants in the VALIANT trial.¹ These data are provided below from Table 3.16 to 3.18. Additional tabulated data from Table 3.19 onwards was provided by the company in response to clarification requests for subgroup data.

Briefly, patient characteristics at baseline were generally between treatment groups however some noticeable differences at the 5% level were evident. Ethnicity differences were evident between groups. The placebo group had less Hispanic participants than the pegcetacoplan group (16.4% vs 23.8%) and more of those participants defined as ‘Not Hispanic or Latino’ (77% vs 65.1%). There were also more participants in the pegcetacoplan group who were of unreported ethnicity.

Table 3.16: VALIANT Baseline demographics (ITT set)

	Pegcetacoplan (N=63), n (%)	Placebo (N=61), n (%)	Overall (N=124), n (%)
Age at screening (years), n	63	61	124
Mean (SD)	28.2 (17.1)	23.6 (14.3)	26.0 (15.9)
Median	19.0	19.0	19.0
Q1, Q3	15.0, 45.0	16.0, 26.0	15.0, 27.0
Min, max	12, 62	12, 74	12, 74
Age group: adolescent (12-17 years), n (%)	28 (44.4)	27 (44.3)	55 (44.4)
Age group: adult (≥18 years), n (%)	35 (55.6)	34 (55.7)	69 (55.6)
Sex, n (%)			
Male	26 (41.3)	28 (45.9)	54 (43.5)
Female	37 (58.7)	33 (54.1)	70 (56.5)
Race, n (%)			
White	45 (71.4)	46 (75.4)	91 (73.4)
Asian	9 (14.3)	9 (14.8)	18 (14.5)
Black or African American	1 (1.6)	0	1 (0.8)
American Indian or Alaskan Native	1 (1.6)	0	1 (0.8)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	7 (11.1)	6 (9.8)	13 (10.5)
Ethnicity, n (%)			
Hispanic	15 (23.8)	10 (16.4)	25 (20.2)
Not Hispanic or Latino	41 (65.1)	47 (77.0)	88 (71.0)
Not reported ^a	6 (9.5)	2 (3.3)	8 (6.5)
Unknown	1 (1.6)	2 (3.3)	3 (2.4)

Adapted from Table 11, CS¹

^a Some participants with ethnicity not reported because some countries do not allow the collection of ethnicities. CS = company submission; ITT = intention-to-treat; Q1 = first quartile; Q3 = third quartile; SD = standard deviation

Baseline disease characteristics for the ITT set are summarised in Table 3.17. 81.0% in the pegcetacoplan group, and 73.8% in the placebo group had C3G underlying disease based on screening biopsy; 19.0% of participants in the pegcetacoplan group and 26.2% in the placebo group had IC-MPGN underlying disease, based on screening biopsy. Medical history characteristics were balanced. Collection of medical history data showed that participants in the placebo group had more genetic risk factors for C3G/IC-MPGN (16.4%) than participants in the pegcetacoplan group (6.3%). Mean (standard deviation, SD) baseline proteinuria assessments (measured by 24-hour collection and triplicate first morning urine [FMU]) were slightly higher in the pegcetacoplan group (baseline 24-hour uPCR: 3,954.7mg/g (2,887.6); baseline triplicate FMU: 3,123.8 mg/g (2,408.3)) than in the placebo group (baseline 24-hour uPCR: 3,290.1 (2,357.5); baseline triplicate FMU: 2,540.8 (2,014.6)). Mean (SD) baseline eGFR was slightly lower in the pegcetacoplan group (78.5 [34.1] mL/min/1.73 m²)¹. than the placebo group (87.3 [37.1] L/min/1.73 m²)¹.

Table 3.17: VALIANT Baseline disease characteristics (ITT set)

	Pegcetacoplan (N=63)	Placebo (N=61)	Overall (N=124)
Underlying disease based on screening biopsy, n (%)			
C3G	51 (81.0)	45 (73.8)	96 (77.4)
C3GN	45 (71.4)	41 (67.2)	86 (69.4)
DDD	4 (6.3)	4 (6.6)	8 (6.5)
Undetermined	2 (3.2)	0	2 (1.6)
IC-MPGN	12 (19.0)	16 (26.2)	28 (22.6)
Indication per disease specific medical history form, n (%)			
C3G	47 (74.6)	48 (78.7)	95 (76.6)
C3GN	43 (68.3)	43 (70.5)	86 (69.4)
DDD	4 (6.3)	4 (6.6)	8 (6.5)
Undetermined	0	1 (1.6)	1 (0.8)
IC-MPGN	16 (25.4)	13 (21.3)	29 (23.4)
Potential risk factors for C3G/IC-MPGN, n (%)			
Genetic risk factors	4 (6.3)	10 (16.4)	14 (11.3)
Autoantibodies	12 (19.0)	9 (14.8)	21 (16.9)
Other	8 (12.7)	8 (13.1)	16 (12.9)
Disease manifestations, n (%)			
Oedema	45 (71.4)	32 (52.5)	77 (62.1)
Fatigue	16 (25.4)	8 (13.1)	24 (19.4)
Haematuria	37 (58.7)	39 (63.9)	76 (61.3)
High blood pressure	35 (55.6)	29 (47.5)	64 (51.6)
Hyperlipidaemia	24 (38.1)	19 (31.1)	43 (34.7)
Nephrotic syndrome	32 (50.8)	27 (44.3)	59 (47.6)
Proteinuria	58 (92.1)	55 (90.2)	113 (91.1)
Reduced GFR	21 (33.3)	14 (23.0)	35 (28.2)
Baseline 24h uPCR (mg/g), n	63	61	124
Mean (SD)	3954.7 (2887.6)	3290.1 (2357.5)	3627.8 (2650.6)
Median	3151.0		2861.0
Q1, Q3	2019.0, 5164.0	2450.0	1822.0, 4774.5
Min, max	631.0, 14624.0	1633.0, 4236.0	631.0, 14624.0

	Pegcetacoplan (N=63)	Placebo (N=61)	Overall (N=124)
		730.0, 14351.0	
Baseline triplicate FMU uPCR (mg/g)^a, n			
Mean (SD)	63	61	124
Median	3123.8 (2408.3)	2540.8	2836.9 (2233.6)
Q1, Q3	2389.2	(2014.6)	2031.3
Min, max	1502.7, 3779.9	1815.6	1287.2, 3544.6
	713.6, 11418.0	1156.4, 3009.6	713.6, 11418.0
		783.4, 10439.0	
Baseline eGFR (mL/min/1.73 m²), n			
Mean (SD)	63	61	124
Median	78.5 (34.1)	87.3 (37.1)	82.8 (35.8)
Q1, Q3	78.0	91.0	85.5
Min, max	47.0, 106.0	52.0, 122.0	50.5, 110.5
	25, 161	24, 156	24, 161
Baseline serum creatinine (mg/dL), n			
Mean (SD)	63	61	124
Median	1.1 (0.6)	1.1 (0.7)	1.1 (0.6)
Q1, Q3	0.99	0.8	0.9
Min, max	0.7, 1.6	0.7, 1.3	0.7, 1.4
	0.5, 2.7	0.4, 3.0	0.4, 3.0
Baseline serum C3 (mg/dL), n			
Mean (SD)	63	61	124
Median	60.6 (45.7)	56.3 (35.6)	58.5 (40.9)
Q1, Q3	60.0	60.0	60.0
Min, max	15.0, 100.0	20.0, 80.0	15.0, 92.5
	10.0, 160.0	10.0, 130.0	10.0, 160.0
Baseline serum albumin (g/dL), n			
Mean (SD)	63	61	124
Median	3.3 (0.6)	3.4 (0.7)	3.3 (0.6)
Q1, Q3	3.35	3.4	3.4
Min, max	2.9, 3.7	2.9, 3.9	2.9, 3.9
	1.8, 4.5	1.9, 4.6	1.8, 4.8
Adapted from Table 12 = CS ¹			
^a The baseline uPCR reported was the result of the average of up to nine values collected.			
C3GN = C3 glomerulonephritis; CS = company submission; DDD = dense deposit disease; eGFR = estimated glomerular filtration rate; FMU = first-morning spot urine; GFR = glomerular filtration rate; h = hour; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; ITT = intention-to-treat; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; uPCR = urinary protein to creatinine ratio			

Baseline characteristics by transplant history for the ITT set are summarised in Table 3.18. Baseline disease characteristics for the post-transplant and non-transplant subgroups generally reflect the overall ITT set. When stratifying by transplant status, the non-transplant population had higher mean and median uPCR from 24-hour urine and average FMU, and the post-transplant population had lower mean and median eGFR compared to the overall ITT set. Differences >5% were evident in underlying disease based on screening biopsy, genetic risk factors, and across various aspects of disease manifestations between the placebo groups and pegcetacoplan groups in both transplant status stratification.

Table 3.18: VALIANT Baseline disease characteristics by transplant status (ITT set)

	Non-transplant		Post-transplant	
	Pegcetacoplan (N=58)	Placebo (N=57)	Pegcetacoplan (N=5)	Placebo (N=4)
Years since diagnosis^a, n				
Mean (SD)	3.8 (3.5)	3.9 (3.7)	1.4 (1.5)	1.4 (1.6)
Median	3.29	3.28	0.51	0.73
Min; max	0.34; 18.40	0.03; 18.63	0.35; 3.57	0.31; 3.77
Underlying disease based on screening biopsy, n (%)				
C3G	46 (79.3)	42 (73.7)	5 (100)	3 (75.0)
C3GN	42 (72.4)	38 (66.7)	3 (60.0)	3 (75.0)
DDD	2 (3.4)	4 (7.0)	2 (40.0)	0
Undetermined	2 (3.4)	0	0	0
IC-MPGN	12 (20.7)	15 (26.3)	0	1 (25.0)
Potential causes of C3G/IC-MPGN, n (%)				
Genetic risk factors	4 (6.9)	9 (15.8)	0	1 (25.0)
Autoantibodies	9 (15.5)	8 (14.0)	3 (60.0)	1 (25.0)
Other	7 (12.1)	7 (12.3)	1 (20.0)	1 (25.0)
uPCR from 24-hour urine (mg/g), n				
Mean (SD)	4092.8 (2964.7)	3413.1 (2385.5)	2353.4 (716.0)	1537.2 (738.6)
Median	3264.0	2571.0	2301.0	1542.5
Min; max	631.0; 14,264.0	1035, 14,351.0	1401.0; 3299.0	730.0; 2334.0
Mean of triplicate FMU UPCR (mg/g)^b, n				
Mean (SD)	3202.1 (2483.3)	2618.9 (2057.3)	2215.0 (951.4)	1426.4 (631.0)
Median	2393.4	1850.5	1845.0	1243.0
Min; max	713.6; 11,418.0	783.4; 10,439.0	1266.4; 3315.1	895.3; 2324.2
eGFR (mL/min/1.73 m²), n				
Mean (SD)	80.1 (34.7)	90.6 (36.0)	59.8 (20.9)	39.5 (13.2)
Median	82.5	95.0	63.0	37.5
Min; max	25; 161	24; 156	34; 81	27; 56
Serum creatinine (mg/dL), n				
Mean (SD)	1.1 (0.6)	1.0 (0.6)	1.4 (0.7)	2.1 (0.7)
Median	0.9	0.8	1.3	2.1
Min; max	0.45; 2.71	0.43; 2.77	0.73; 2.35	1.32; 3.01
Serum albumin (g/dL), n				
Mean (SD)	3.3 (0.6)	3.3 (0.7)	3.6 (0.3)	4.0 (0.6)
Median	3.2	3.3	3.5	3.9

	Non-transplant		Post-transplant	
	Pegcetacoplan (N=58)	Placebo (N=57)	Pegcetacoplan (N=5)	Placebo (N=4)
Min; max	1.8; 4.6	1.9; 4.5	3.4; 4.0	3.5; 4.8
Time since last kidney transplant (years), n				
Mean (SD)	N/A	N/A	11.4 (6.7)	5.8 (6.4)
Median	N/A	N/A	11.3	3.3
Min; max	N/A	N/A	3.8; 19.1	1.5; 15.4
Total number of kidney transplants, n (%)				
1	N/A	N/A	4 (80)	4 (100)
2	N/A	N/A	1 (20)	0
Did participant receive prior dialysis? n (%)				
Yes	1 (1.7)	0	3 (60.0)	3 (75.0)
No	57 (98.3)	57 (100)	2 (40.0)	1 (25.0)
Time since most recent post-transplant recurrence (years), n				
Mean (SD)	N/A	N/A	1.5 (1.5)	1.4 (1.6)
Median	N/A	N/A	0.5	0.7
Min; max	N/A	N/A	0.4; 3.6	0.3; 3.8
Time from last kidney transplant to the most recent post-transplant recurrence (years), n				
Mean (SD)	N/A	N/A	9.9 (7.1)	4.4 (7.1)
Median	N/A	N/A	10.8	1.2
Min; max	N/A	N/A	2.3, 18.7	0.2, 15.0
Disease manifestations, n				
Oedema	42 (72.4)	30 (52.6)	3 (60.0)	2 (50.0)
Fatigue	16 (27.6)	8 (14.0)	0	0
Haematuria	34 (58.6)	37 (64.9)	3 (60.0)	2 (50.0)
High blood pressure	30 (51.7)	25 (43.9)	5 (100)	4 (100)
Hyperlipidaemia	22 (37.9)	18 (31.6)	2 (40.0)	1 (25.0)
Nephrotic syndrome	30 (51.7)	25 (43.9)	2 (40.0)	2 (50.0)
Proteinuria	53 (91.4)	51 (89.5)	5 (100)	4 (100)
Reduced GFR	17 (29.3)	11 (19.3)	4 (80.0)	3 (75.0)

Adapted from Table 13, CS¹

^a For post-transplant participants, the date of diagnosis refers to the most recent post-transplant recurrence (based on medical history).

^b The triplicate FMU uPCR reported was the result of the average of up to 9 values collected.

C3G = C3 glomerulopathy; C3GN = C3 glomerulonephritis; CS = company submission; DDD = dense deposit disease; eGFR = estimated glomerular filtration rate; FMU = first morning urine; GFR = glomerular filtration rate; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; ITT = intention-to-treat; n = number of unique participants in statistic; N = number of participants in study group; N/A = not applicable; SD = standard deviation; uPCR = urinary protein to creatinine ratio

The CS provides text stating baseline biopsy characteristics were generally balanced between groups with the exception of glomerular crescents which were absent for 96.8% in the pegcetacoplan group vs 90.2% in the placebo group.¹

Findings related to accepted prognostic indicators for the disease are as follows:

- Mean (SD) total activity score was 7.4 (4.1) in the pegcetacoplan group and 8.2 (3.7) in the placebo group.
- Mean (SD) total chronicity score was 2.5 (2.5) in the pegcetacoplan group and 1.8 (2.0) in the placebo group.

Over 90% of participants in each group were receiving treatment with ACEi/ARB during the RCP (see Table 3.19). In addition, 74.6% of participants in pegcetacoplan group and 68.9% participants in placebo group were receiving immunosuppressants during the RCP. The proportions of participants on systemic corticosteroids (39.7% in the pegcetacoplan group and 39.3% in the placebo group) and SGLT2 inhibitors (11.1% in the pegcetacoplan group and 9.8% in the placebo group) were similar across the treatment groups. Of note, the use of immunosuppressants was balanced between groups and there was no new initiation of treatment with immunosuppressants or systemic corticosteroids. The proportion of participants using the following groups of medications was at least approximately two-fold higher in the pegcetacoplan group: calcium-channel blockers, beta blockers, antihypertensives, and thyroid therapeutics. Conversely, the proportion of participants using mineral supplements was approximately two-fold higher in the placebo group. None of these treatments were expected to have an impact on proteinuria.¹

Table 3.19: VALIANT Concomitant medications as standard of care for during the RCP

	Pegcetacoplan (N=63), n (%)	Placebo (N=61), n (%)	Overall (N=124), n (%)
ACEi/ARB	57 (90.5)	56 (91.8)	113 (91.1)
Immunosuppressants	47 (74.6)	42 (68.9)	89 (71.8)
Mycophenolate mofetil	36 (57.1)	34 (55.7)	70 (56.5)
Mycophenolate sodium	2 (3.2)	4 (6.6)	6 (4.8)
Mycophenolic acid	4 (6.3)	1 (1.6)	5 (4.0)
Tacrolimus	12 (19.0)	11 (18.0)	23 (18.5)
Tacrolimus monohydrate	0	1 (1.6)	1 (0.8)
Ciclosporin	0	1 (1.6)	1 (0.8)
Tocilizumab	1 (1.6)	0	1 (0.8)
Corticosteroids for systemic use	25 (39.7)	24 (39.3)	49 (39.5)
Prednisone	17 (27.0)	16 (26.2)	33 (26.6)
Prednisolone	8 (12.7)	5 (8.2)	13 (10.5)
Deflazacort	0	1 (1.6)	1 (0.8)
Hydrocortisone	0	1 (1.6)	1 (0.8)
Meprednisone	0	1 (1.6)	1 (0.8)
Methylprednisolone	0	1 (1.6)	1 (0.8)
Prednisolone hemisuccinate	0	1 (1.6)	1 (0.8)
SGLT2 inhibitors	7 (11.1)	6 (9.8)	13 (10.5)
Dapagliflozin	3 (4.8)	4 (6.6)	7 (5.6)

	Pegcetacoplan (N=63), n (%)	Placebo (N=61), n (%)	Overall (N=124), n (%)
Dapagliflozin propanediol monohydrate	4 (6.3)	1 (1.6)	5 (4.0)
Empagliflozin	0	1 (1.6)	1 (0.8)
Adapted from Table 14, CS ¹ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CS = company submission; RCP = randomised controlled period; SGLT2 = sodium-glucose cotransporter-2			

Concomitant medications for the safety set during the OLP are summarised in Table 3.20. 100% of participants who continued in the OLP, across both pegcetacoplan and placebo groups, had at least one recorded concomitant medication. The most frequently reported immunosuppressive concomitant medications by Preferred Term (PT) were mycophenolate mofetil 55.1% and tacrolimus 17.8%.¹

Table 3.20: Concomitant medications for the OLP (OLP set)

	Pegcetacoplan-to-pegcetacoplan (N=61), n (%)	Placebo-to-pegcetacoplan (N=57), n (%)	Overall (N=118), n (%)
Any concomitant medications	61 (100)	57 (100)	118 (100)
ACEi/ARB	58 (95.1)	52 (91.2)	110 (93.2)
Immunosuppressants	43 (70.5)	39 (68.4)	82 (69.5)
Mycophenolate mofetil	33 (54.1)	32 (56.1)	65 (55.1)
Tacrolimus	11 (18.0)	10 (17.5)	21 (17.8)
Mycophenolate sodium	2 (3.3)	5 (8.8)	7 (5.9)
Mycophenolic acid	3 (4.9)	1 (1.8)	4 (3.4)
Azathioprine	2 (3.3)	0	2 (1.7)
Tacrolimus monohydrate	0	1 (1.8)	1 (0.8)
Corticosteroids for systemic use	23 (37.7)	23 (40.4)	46 (39.0)
Prednisone	14 (23.0)	14 (24.6)	28 (23.7)
Prednisolone	8 (13.1)	6 (10.5)	14 (11.9)
Betamethasone; desloratadine	0	1 (1.8)	1 (0.8)
Cortisone	0	1 (1.8)	1 (0.8)
Deflazacort	0	1 (1.8)	1 (0.8)
Hydrocortisone	0	1 (1.8)	1 (0.8)
Meprednisone	0	1 (1.8)	1 (0.8)
Triamcinolone acetonide	1 (1.6)	0	1 (0.8)
SGLT2 inhibitors	7 (11.5)	7 (12.3)	14 (11.9)
Dapagliflozin	3 (4.9)	4 (7.0)	7 (5.9)
Dapagliflozin propanediol monohydrate	3 (4.9)	1 (1.8)	4 (3.4)
Empagliflozin	0	1 (1.8)	1 (0.8)
Gemigliptin tartrate; metformin hydrochloride	0	1 (1.8)	1 (0.8)
Sitagliptin	1 (1.6)	0	1 (0.8)

	Pegcetacoplan-to-pegcetacoplan (N=61), n (%)	Placebo-to-pegcetacoplan (N=57), n (%)	Overall (N=118), n (%)
Adapted from Table 15, CS ¹ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CS = company submission; OLP = open-label period; SGLT2 = sodium-glucose cotransporter-2			

The EAG requested additional information from the company on concomitant medications in the following subgroups:

- I. Primary C3G pre-transplant
- II. Primary C3G post-transplant
- III. Primary IC-MPGN pre-transplant
- IV. Primary IC-MPGN post-transplant

In their response to clarification,⁸ the company provided the following Tables.

Table 3.21: Concomitant medications as standard of care during the RCP (C3G pre-transplant)

	Pegcetacoplan (N=46), n (%)	Placebo (N=42), n (%)	Overall (N=88), n (%)
ACEi/ARB	43 (93.5)	37 (88.1)	80 (90.9)
Immunosuppressants	32 (69.6)	27 (64.3)	59 (67.0)
Corticosteroids for systemic use	17 (37.0)	12 (28.6)	29 (33.0)
SGLT2 inhibitors	7 (15.2)	3 (7.1)	10 (11.4)
Adapted from company response to clarification ⁸ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; C3G = C3 glomerulopathy; RCP = randomised controlled period; SGLT2 = sodium-glucose cotransporter-2			

Some marked differences beyond 5% were evident with more use in the pegcetacoplan arm of all medications except ACEi/ARB (see Table 3.21) and of ACEi/ARB in the pegcetacoplan-to-pegcetacoplan group (see Table 3.22).

Table 3.22: Concomitant medications as standard of care during the OLP (C3G pre-transplant)

	Pegcetacoplan-to-pegcetacoplan (N=44), n (%)	Placebo-to-pegcetacoplan (N=38), n (%)	Overall (N=82), n (%)
ACEi/ARB	42 (95.5)	33 (86.8)	75 (91.5)
Immunosuppressants	28 (63.6)	24 (63.2)	52 (63.4)
Corticosteroids for systemic use	14 (31.8)	11 (28.9)	25 (30.5)
SGLT2 inhibitors	5 (11.4)	3 (7.9)	8 (9.8)
Adapted from company response to clarification ⁸ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; C3G = C3 glomerulopathy; OLP = open label period; SGLT2 = sodium-glucose cotransporter-2			

Table 3.23: Concomitant medications as standard of care during the RCP (C3G post-transplant)

	Pegcetacoplan (N=5), n (%)	Placebo (N=3), n (%)	Overall (N=8), n (%)
ACEi/ARB	4 (80.0)	3 (100.0)	7 (87.5)

Immunosuppressants	5 (100.0)	3 (100.0)	8 (100.0)
Corticosteroids for systemic use	5 (100.0)	3 (100.0)	8 (100.0)
SGLT2 inhibitors	1 (20.0)	1 (33.3)	2 (25.0)
Adapted from company response to clarification ⁸ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; C3G = C3 glomerulopathy; RCP = randomised controlled period; SGLT2 = sodium-glucose cotransporter-2			

Table 3.24: Concomitant medications during the OLP (C3G post-transplant)

	Pegcetacoplan (N=5), n (%)	Placebo, (N=3), n (%)	Overall (N=8), n (%)
ACEi/ARB	5 (100.0)	3 (100.0)	8 (100.0)
Immunosuppressants	5 (100.0)	3 (100.0)	8 (100.0)
Corticosteroids for systemic use	5 (100.0)	3 (100.0)	8 (100.0)
SGLT2 inhibitors	1 (20.0)	1 (33.3)	2 (25.0)
Adapted from Company response to clarification ⁸ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; C3G = C3 glomerulopathy; OLP = open label period; SGLT2 = sodium-glucose cotransporter-2			

Table 3.25: Concomitant medications as standard of care for during the RCP (Primary IC-MPGN pre-transplant)

	Pegcetacoplan (N=12), n (%)	Placebo (N=15), n (%)	Overall (N=27), n (%)
ACEi/ARB	10 (83.3)	15 (100.0)	25 (92.6)
Immunosuppressants	10 (83.3)	11 (73.3)	21 (77.8)
Corticosteroids for systemic use	4 (33.3)	8 (53.3)	12 (44.4)
SGLT2 inhibitors	1 (8.3)	1 (6.7)	2 (7.4)
Adapted from Company response to clarification ⁸ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; RCP = randomised controlled period; SGLT2 = sodium-glucose cotransporter-2			

Table 3.26: Concomitant medications for the OLP (Primary IC-MPGN pre-transplant)

	Pegcetacoplan (N=12), n (%)	Placebo (N=15), n (%)	Overall (N=27), n (%)
ACEi/ARB	10 (83.3)	11 (73.3)	21 (77.8)
Immunosuppressants	7 (58.3)	9 (60.0)	16 (59.3)
Corticosteroids for systemic use	3 (25.0)	7 (46.7)	10 (37.0)
SGLT2 inhibitors	1 (8.3)	1 (6.7)	2 (7.4)
Adapted from company response to clarification ⁸ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; OLP = open label period; SGLT2 = sodium-glucose cotransporter-2			

Table 3.27: Concomitant medications as standard of care for during the RCP (Primary IC-MPGN post-transplant)

	Pegcetacoplan (N=0), n (%)	Placebo (N=1), n (%)	Overall (N=1), n (%)
ACEi/ARB	0 (0.0)	1 (100.0)	1 (100.0)
Immunosuppressants	0 (0.0)	1 (100.0)	1 (100.0)
Corticosteroids for systemic use	0 (0.0)	1 (100.0)	1 (100.0)
SGLT2 inhibitors	0 (0.0)	1 (100.0)	1 (100.0)
Adapted from company response to clarification ⁸ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; RCP = randomised controlled period; SGLT2 = sodium-glucose cotransporter-2			

Table 3.28: Concomitant medications for the OLP (Primary IC-MPGN post-transplant)

	Pegcetacoplan (N=0), n (%)	Placebo (N=1), n (%)	Overall (N=1), n (%)
ACEi/ARB	0 (0.0)	1 (100.0)	1 (100.0)
Immunosuppressants	0 (0.0)	1 (100.0)	1 (100.0)
Corticosteroids for systemic use	0 (0.0)	1 (100.0)	1 (100.0)
SGLT2 inhibitors	0 (0.0)	1 (100.0)	1 (100.0)
Adapted from company response to clarification ⁸ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; OLP = open label period; SGLT2 = sodium-glucose cotransporter-2			

The EAG also requested that similar data for England and Wales clinical practice was provided, and the company comment on the comparison between these data and those for the VALIANT trial. In their response to clarification, the company stated that ‘... *medication use for C3G and IC-MPGN in UK clinical practise was extracted from a publication reporting from the RaDaR registry*’. The company go on to state that ‘*Of the 371 incident patients enrolled in the RaDaR registry, 38% (n=42) with C3GN, 42% (n=22) with dense deposit disease (DDD) and 49% (n=63) of those with IC-MPGN had used immunosuppression within 1-yr of diagnosis. A RAS inhibitor was used by 40% (n=44) with C3GN, 43% (n=23) with DDD and 42% (n=54) with IC-MPGN, within 1-yr of diagnosis*’.⁸

The company acknowledge that concomitant medication use in VALIANT was higher overall compared to the Rare Disease Registry (RaDaR) study but attempt to mitigate this by emphasising that the RaDaR study listed medication use within one year of diagnosis and not the overall number on standard of care at data collection, making it difficult to compare with the VALIANT trial.⁸

The company also make the point that it ‘*It is notable that whilst immunosuppressant use was high in VALIANT (65% of patients with C3G and 67% with IC-MPGN) a subgroup analysis of patients in VALIANT on concomitant immunosuppressive (IS) therapy, demonstrated favourable efficacy regardless of their IS treatment status. Both groups achieved eGFR stabilization (+6.8 and +5.0 mL/min/1.73 m² vs placebo in IS-treated and non IS-treated patients, respectively and there was a 70.3% and 64.5% clinically meaningful proteinuria reduction vs placebo in IS-treated and non IS-treated patients, respectively)*’.⁸

They further note that ‘The number of post-transplant patients from the VALIANT study were small (n=8 for C3G and n=1 for IC-MPGN). All post-transplant patients were on immunosuppressant therapy, but the proportion on a RAS inhibitor was similar to the pre-transplant group. As the RaDaR study did not segregate pre-and post-transplant it is not possible to comment on how these data compare with UK clinical practice’.⁸

EAG comment: There are some concerns with the matching of the arms with noticeable differences at 5% or above across of range of characteristics, including but not limited to ethnicity, C3G underlying disease at baseline, genetic risk factors, autoantibody presence, eGFR values, and disease manifestations. Many of these imbalances are also evident when considered by transplant status/subgroup. While we do not claim that such differences are clinically meaningful and, in some cases, may exist only as a consequence of a small sample size, it should be considered when interpreting results. The EAG also notes some imbalances between the participant data and the RaDaR registry, particularly with regards to concomitant medications. The company offer mitigation to such an issue, but regardless we highlight this.

3.2.4.2 NOBLE baseline characteristics

The company provide details of the NOBLE baseline characteristics in appendix J of the CS.⁷ A summary of these data are provided in the Tables below.

The company emphasise that the mean age, weight, height, body mass index (BMI), systolic blood pressure, and diastolic blood pressure at baseline were similar and balanced between group 1 and group 2.⁷ There were also several differences between groups beyond the 5% level but given the small sample sizes these differences cannot be assumed to reflect any meaningful sample differences.

Table 3.29: Baseline demographics for participants in NOBLE (ITT set)

	Group 1 (N=10), n (%)	Group 2 (N=3), n (%)	Overall (N=13), n (%)
Age at screening (years)			
Mean (SD)	39.8 (12.8)	44.33 (19.2)	40.8 (14.8)
Median	35	43	36
Q1, Q3	33,49	21,69	33,49
Min, max	20,64	21,69	20,69
Age group: ≤65 years, n (%)	10 (100)	2 (66.7)	12 (92.3)
Sex, n (%)			
Male	5 (50)	2 (66.7)	7 (53.8)
Female	5 (50)	1 (33.3)	6 (46.2)
Race, n (%)			
White	9 (90%)	3 (100%)	12 (92.31%)
Ethnicity, n (%)			
Hispanic	9 (90%)	2 (66.7%)	10 (76.9%)
Not Hispanic or Latino	1 (10%)	1 (33.3%)	3 (23.1%)
Baseline weight (kg) n	10	3	13
Mean (SD)	66.8 (9.3)	70.3 (18.0)	67.6 (11.0)
Median	68.0	76.4	69.0
Q1, Q3	58.0, 71.8	50.0, 84.4	58.0, 76.4
Min, Max	53.8, 81.0	50.0	50.0, 84.4

	Group 1 (N=10), n (%)	Group 2 (N=3), n (%)	Overall (N=13), n (%)
Baseline BMI (kg/m²) n	10	3	13
Mean (SD)	135.7 (16.1)	24.5 (5.4)	23.7 (3.5)
Median	24.0	26.6	24.9
Q1, Q3	21.3, 25.5	18.4, 28.6	21.3, 26.1
Min, Max	18.5, 27.9	18.4, 28.6	18.4, 28.6
Baseline systolic blood pressure (mm/Hg), n	10	3	13
Mean (SD)	135.7 (16.1)	138.0 (13.0)	136.2 (14.9)
Median	134.5	131.0	131.0
Q1, Q3	125.0, 145.0	130.0, 153.0	130.0, 145.0
Min, Max	111, 168	130, 153	111, 168
Baseline diastolic blood pressure (mm/Hg), n	10	3	13
Mean (SD)	84.7 (10.6)	73.7 (8.0)	82.2 (10.9)
Median	80.5	73.0	80.0
Q1, Q3	79.0, 98.0	66.0, 82.0	78.0, 83.0
Min, Max	69, 101	66.8	66, 101
Adapted from Table 132, CS appendix J ⁷ Baseline is defined as the most recent non-missing measurement prior to first study drug dose for group 1 subjects or randomisation for group 2 subjects. Because some countries do not allow the collection of race, there are some subjects with race not reported. BMI (kg/m ²) = Weight (kg)/(Height(m)) ² BMI = body mass index; CS = company submission; ITT = intention-to-treat; Q1 = first quartile; Q3 = third quartile; SD = standard deviation			

Baseline disease characteristics are summarised for the ITT set in Table 3.30. 30.8% of C3G/IC-MPGN were attributed to genetic risk factors, followed by autoantibodies (23.1%) and reason classified as “other” (7.7%). Disease manifestations across both groups included high blood pressure (92.3%), proteinuria (92.3%), haematuria (76.9%), and reduced GFR (53.8%).

Most participants had one kidney transplant (69.2%), while 3 participants (23.1%) had two kidney transplants and 1 participant (7.7%) received three transplants. 84/6% of participants received prior dialysis. Proteinuria assessed by mean (SD) uPCR from 24-hour urine was 1,549.6 (960.8) mg/g in group 1 and 2,078.7 (1,403.3) mg/g in group 2. Similar results were observed in uPCR from triplicate spot urine. The observed eGFR, serum creatinine, and serum albumin were similar across both groups. Mean (SD) time since most recent post-transplant recurrence of C3G or IC-MPGN was 0.9 (0.9) years in group 1 and 2.8 (2.4) years in group 2, reflecting that participants in group 2 have longer recurrent diseases than in group 1.⁷

Table 3.30: Baseline disease characteristics for participants in NOBLE (ITT set)

	Group 1 (N=10)	Group 2 (N=3)	Overall (N=13)
Underlying Disease based on screening biopsy			
C3G, n (%)	8 (80.0)	2 (66.7)	10 (76.9)
C3GN, n (%)	5 (50.0)	2 (66.7)	7 (53.8)
DDD, n (%)	2 (20.0)	0	2 (15.4)
Undetermined, n (%)	1 (10.0)	0	1 (7.7)
IC-MPGN, n (%)	2 (20.0)	1 (33.3)	3 (23.1)

	Group 1 (N=10)	Group 2 (N=3)	Overall (N=13)
Underlying disease per medical history			
C3G, n (%)	8 (80.0)	1 (33.3)	9 (69.2)
C3GN, n (%)	6 (60.0)	1 (33.3)	7 (53.8)
DDD, n (%)	2 (20.0)	0	2 (15.4)
IC-MPGN, n (%)	2 (20.0)	2 (66.7)	4 (30.8)
Time since last kidney transplant (years)^a			
n	10	3	13
Mean (SD)	1.9 (1.3)	5.5 (0.5)	2.7 (1.9)
Median	1.5	5.5	2.4
Q1, Q3	0.8, 2.6	5.3, 5.6	1.1, 4.9
Min, max	0.6, 4.9	4.9, 5.8	0.6, 5.8
Total number of kidney transplants^b			
1, n (%)	7 (70.0)	2 (66.7)	9 (69.2)
2, n (%)	2 (20.0)	1 (33.3)	3 (23.1)
3, n (%)	1 (10.0)	0 (0.0)	1 (7.7)
24hr UPCR (mg/g)			
n	10	3	13
Mean (SD)	1549.9 (960.6)	2078.7 (1403.6)	1671.92(1036.5)
Median	1400	1875	1490
Q1, Q3	1099.0, 2020.0	832.0, 3599.0	1099.0, 2020.0
Min, max	239.0, 3062.0	832.0, 3599.0	239.0, 3599.0
Triplicate spot urine uPCR (mg/g)^c			
n	10	3	13
Mean (SD)	1523.4 (1033.8)	2314.9 (2170.7)	1706.1 (1307.8)
Median	1688.8	1711.3	1703.7
Q1, Q3	506.7, 2185.8	509.7, 4723.3	509.7, 2185.8
Min, max	203.7, 2984.0	507.9, 4723.3	203.7, 4723.3
eGFR (mL/min/1.73 m²)			
n	10	3	13
Mean (SD)	50.9 (12.7)	53.3 (11.3)	51.5 (12.0)
Median	47	50	50
Q1, Q3	44.0, 56.0	44.0, 66.0	42.0, 65.0
Min, max	35.1, 71.4	44.0, 66.0	35.1, 71.4
Serum creatinine (mg/dL)			
n	10	3	13
Mean (SD)	1.6 (0.3)	1.5 (0.1)	1.5 (0.3)
Median	1.5	1.5	1.6
Q1, Q3	1.4, 1.7	1.3, 1.6	1.4, 1.7
Min, max	1.0, 2.1	1.2, 1.6	1.0, 2.1

	Group 1 (N=10)	Group 2 (N=3)	Overall (N=13)
Serum albumin (g/dL)			
n	10	3	13
Mean (SD)	4.1 (0.5)	3.6 (0.4)	3.9 (0.5)
Median	3.9	3.6	3.9
Q1, Q3	3.7, 4.5	3.2, 4.1	3.6, 4.5
Min, max	3.2, 5.0	3.2, 4.1	3.2, 5.0
Serum C3 (mg/dL)^d			
n	10	3	13
Mean (SD)	60.8 (35.2)	100.3 (48.2)	69.9 (40.2)
Median	72.5	95.0	75.0
Q1, Q3	42.0, 84.0	55.0, 151.0	55.0, 88.0
Min, max	1.0, 103.0	55.0, 151.0	1.0, 151.0
Time since most recent post-transplant recurrence (years)^e			
n	10	3	13
Mean (SD)	0.9 (0.9)	2.8 (2.4)	1.4 (1.5)
Median	0.6	2.4	0.7
Q1, Q3	0.4, 1.6	0.6, 5.4	0.4, 1.6
Min, max	0.2, 3.0	0.6, 5.4	0.2, 5.4
Adapted from Table 133, CS appendix J ⁷ ^a Time since last kidney transplant (years) = (day 1 date – date of last kidney transplant)/365.25. ^b Percentage was based on number of participants with kidney transplant. ^c The uPCR reported for each participant was the result of the average of the triplicate first morning spot urine test. ^d C3 values reported as BLQ were taken as half of the lower limit of quantification (LLOQ/2), where LLOQ was 2 mg/dL. ^e Time since most recent post-transplant recurrence (years) = (day 1 date – date of post-transplant recurrence)/365.25. Note: Baseline was defined as the most recent non missing measurement prior to first IP dose for group 1 participants or randomisation for group 2 participants. BLQ = below the limit of quantification; C3G = complement 3 glomerulopathy; C3GN = C3 glomerulonephritis; CS = company submission; DDD = dense deposit disease; eGFR = estimated glomerular filtration rate; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; ITT = intention-to-treat; LLOQ = lower limit of quantification; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; uPCR = urinary protein to creatinine ratio			

Baseline biopsy characteristics are summarised for the ITT set in Table 3.31. 40.0% in group 1 and no participants in group 2 having glomerular crescents present on the baseline biopsy. Of note, none of the observed crescents were fibrous crescents. Interstitial fibrosis and tubular atrophy were mostly <10% in group 1 and mostly between 10% and 25% in group 2. The baseline biopsy characteristics data suggest that participants in group 1 have higher disease activity and lower chronic pathologic changes on baseline biopsy than participants in group 2. Banff score at baseline indicated absence of rejection in all 13 participants (100%).⁷

Table 3.31: Baseline biopsy characteristics for participants in NOBLE (ITT set)

	Group 1 (N=10)	Group 2 (N=3)	Overall (N=13)
C3c staining, n (%)			
0	0	0	0
1	0	0	0
2	1 (10.0)	1 (33.3)	2 (15.4)
3	9 (90.0)	2 (66.7)	11 (84.6)
Glomerular crescents, n (%)			
Absent			
Present	6 (60.0)	3 (100)	9 (69.2)
Interstitial fibrosis, n (%)			
<10%	8 (80.0)	0	8 (61.5)
10%-25%	1 (10.0)	2 (66.7)	3 (23.1)
26%-50%	1 (10.0)	1 (33.3)	2 (15.4)
>50%	0	0	0
Tubular atrophy, n (%)			
<10%	8 (80.0)	0	8 (61.5)
10%-25%	1 (10.0)	2 (66.7)	3 (23.1)
26%-50%	1 (10.0)	1 (33.3)	2 (15.4)
>50%	0	0	0
Total activity score			
n	10	3	13
Mean (SD)	8.4 (6.7)	3.3 (5.8)	7.2 (6.7)
Median	8.5	0	7.0
Q1, Q3	2.0, 14.0	0.0, 10.0	1.0, 11.0
Min, max	0, 20	0, 10	0, 20
Total chronicity score			
n	10	3	13
Mean (SD)	1.0 (2.3)	4.7 (1.2)	1.8 (2.6)
Median	0	4.0	0
Q1, Q3	0.0, 0.0	4.0, 6.0	0.0, 4.0
Min, max	0, 7	4, 6	0, 7
Adapted from Table 15, appendix J, CS ⁷ CS = company submission; ITT = intention-to-treat; Q1 = first quartile; Q3 = third quartile; SD = standard deviation			

All 13 participants in the safety set had at least one recorded prior medication. Across both groups, the most frequently reported prior medications by Anatomical Therapeutic Chemical (ATC) classification (level 2 included immunosuppressants (100%), agents acting on the renin-angiotensin system (84.6%), and corticosteroids for systemic use (84.6%). The most frequently reported prior medications by PT were mycophenolate mofetil (76.9%) and tacrolimus (76.9%). 76.9% of participants across both groups had at least one recorded concomitant medication. Overall, the most common concomitant medications by ATC level 2 included antibacterials for systemic use (38.5%) and corticosteroids for systemic use

(30.8%). The most frequently reported concomitant medications by PT were phenoxymethylpenicillin, folic acid, mycophenolate mofetil, and paracetamol (15.4% for each PT).⁷

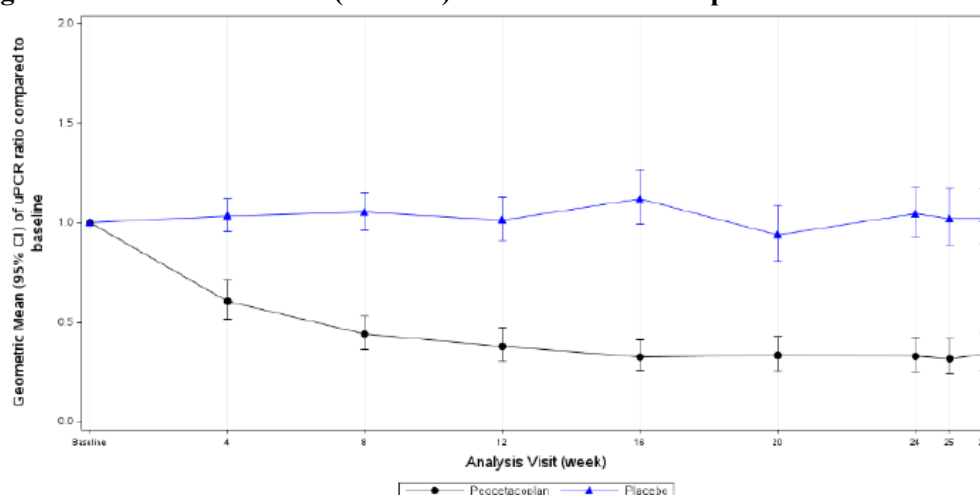
3.2.5 VALIANT study clinical effectiveness

3.2.5.1 Primary efficacy outcome: proteinuria reduction

Log-transformed ratio of uPCR at week 26 compared to baseline

The CS included the following statements: “The difference in LS mean of log-transformed UPCR between pegcetacoplan and placebo was -1.14 (95% CI: -1.44 to -0.85); $P < .0001$. This is equivalent to a relative reduction of 68.1% (95% CI: 57.3%-76.2%) of pegcetacoplan compared to placebo (see Figure 3.6).

Figure 3.6: Geometric mean (95% CI) of uPCR Ratio Compared to Baseline for RCP (ITT set)



Adapted from Figure 6, CS¹

CI = confidence interval; CS = company submission; ITT = intention-to-treat; RCP = randomised controlled period; uPCR = urinary protein to creatinine ratio

3.2.5.2 Secondary efficacy outcomes

Several secondary efficacy findings are presented measured by eGFR in patients with C3G or IC-MPGN. The CS stated that overall, the secondary efficacy outcomes measured demonstrate consistent treatment effects of pegcetacoplan in proteinuria reduction, decrease in C3c staining and kidney function stabilisation (see Table 3.32).¹

Table 3.32: Key secondary efficacy endpoints at Week 26 (ITT set)

Endpoint	Pegcetacoplan	Placebo	Comparison between groups
Proportion of participants achieving the composite renal endpoint (n, %)	N=63 31 (49.2)	N=61 2 (3.3)	Odds ratio (95% CI) 27.48 (6.09-123.85) $P < .0001$
Proportion of participants with $\geq 50\%$ reduction in uPCR (n, %)	N=63 38 (60.3)	N=61 3 (4.9)	Odds ratio (95% CI) 30.901 (8.39-113.77) $P < .0001$
Change in the activity score of the C3G histologic index score	N=35 -3.48	N=34 -2.48	Difference (95% CI) in LS mean -1.00 (-2.80, 0.79)

Endpoint	Pegcetacoplan	Placebo	Comparison between groups
from baseline (LS mean, 95% CI)	(-4.72 to -2.24)	(-3.77 to -1.19)	$P = .2753$
Proportion of participants showing decreases in C3c staining on renal biopsy from baseline (n, %)	N=35 26 (74.3)	N=34 4 (11.76)	Odds ratio (95% CI) 27.39 (6.48-115.85) $P < .0001$
Change in eGFR from baseline (LS mean, 95% CI)	N=63 -1.49 (-5.89, 2.89)	N=61 -7.81 (-11.57 to -4.05)	Difference (95% CI) in LS mean 6.31 (0.50-12.12) $P = .0333$
Adapted from Table 20, CS ¹ ^a The composite renal endpoint was defined as achieving both a stable or improved eGFR compared to baseline (defined as $\leq 15\%$ reduction in eGFR) and a $\geq 50\%$ reduction in uPCR compared to baseline. ^b The logistic model included treatment group as independent variable and adjusted for baseline values, disease type, and stratification factors. A composite strategy was used where the response status at or after the occurrence of any of the intercurrent events was regarded as non-responder. Participants with missing outcome values other than intercurrent events were regarded as non-responder. ^c Renal biopsy endpoints were only evaluated for adult patients. Renal biopsies were not required for participants younger than 18 years of age. C3G = C3 glomerulopathy; CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; ITT = intention-to-treat; LS = least-square; uPCR = urinary protein to creatine ratio			

3.2.5.3 Additional secondary efficacy endpoints

These outcomes are summarised in Table 3.33.

Table 3.33: Results of additional secondary efficacy endpoints at week 26 (ITT set)

Endpoint	Pegcetacoplan	Placebo	Comparison between groups
Proportion of participants achieving proteinuria <1 g/day (n, %)	N=63 23 (36.5)	N=61 7 (11.9)	Odds ratio ^a (95% CI) 5.75 (2.11, 15.72) $P = .0006$
Proportion of participants with baseline serum albumin levels <LLN who achieve normalisation of serum albumin levels (n, %)	N=27 21 (77.8)	N=23 1 (4.4)	Odds ratio ^a (95% CI) 88.34 (8.86, 880.54) $P = .0001$
Proportion of participants with baseline serum C3 levels <LLN who achieve serum C3 levels above LLN (n, %)	N=41 37 (90.2)	N=49 3 (6.1)	$P = .0094$
Change in FACIT-Fatigue Scale score from baseline (LS mean, 95% CI)	N=63 0.93 (-1.56, 3.42)	N=61 0.52 (-1.75, 2.79)	Difference (95% CI) in LS mean ^b 0.41 (-2.85, 3.68) $P = .8054$
Change in KDQOL score from baseline (LS mean, 95% CI)	N=63 0.86 (-2.32, 4.04)	N=61 -0.46 (-3.60, 2.69)	Difference (95% CI) in LS mean ^b 1.31 (-3.18, 5.81) $P = .5664$

Endpoint	Pegcetacoplan	Placebo	Comparison between groups
Adapted from Table 26, CS ¹ ^a The logistic model included treatment group as independent variable and adjusted for baseline values, disease type, and stratification factors. A composite strategy was used where the response status at or after the occurrence of any of the intercurrent events was regarded as non-responder. Participants with missing outcome values other than intercurrent events were regarded as non-responder. ^b Analysis of covariance model included treatment as fixed effect, adjusted for baseline, disease type, and stratification factors. Use of prohibited medications or rescue therapies or start of renal replacement therapy was handled by hypothetical strategy, discontinuation of treatment was handled by treatment policy strategy. CI = confidence interval; CS = company submission; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; KDQOL = Kidney Disease Quality of Life; ITT = intention-to-treat; LLN = lower limit of normal; LS = least-square			

3.2.5.4 Key exploratory efficacy outcomes

3.2.5.4.1 Proportion of participants with normalisation of proteinuria

Compared to the placebo, the group treated with pegcetacoplan showed a statistically significant proportion of normalisation of proteinuria ($p = 0.0006$) (17.5%) versus 0% based on the CS.¹

3.2.5.4.2 Time to 50% reduction in uPCR with a stable or improved eGFR renal composite endpoint

Based on the CS:¹ “the number of participants meeting the definition of the composite renal endpoint 50% reduction in UPCR with a stable or improved eGFR was 44 participants (69.8%) in the pegcetacoplan group and 9 participants (14.8%) in the placebo group. The median (95% CI) time to achievement of the renal composite endpoint was 80 (54-113) days for the pegcetacoplan group (the result was NA for the placebo group) ($P < .0001$). By week 26, 67.7% of participants in the pegcetacoplan group and 13.5% of participants in the placebo group reached this endpoint. Hazard ratio (95% CI) is 8.86 (4.16-18.87) from analysis of time to 50% reduction in UPCR using a Cox proportional hazards model.”

3.2.5.4.3 Change from baseline in EQ-5D-5L score

This is summarised in Table 3.34.

Table 3.34: Analysis of change from baseline at Week 26 in EQ-5D-5L score with ANCOVA model by treatment group (ITT set)

	Pegcetacoplan (N=63)	Placebo (N=61)
Number of subjects included in the model	33	38
Estimates/Comparisons at Week 26		
LS mean (SE)	3.44 (2.15)	2.85 (1.99)
95% CI of LS mean	(-0.853, 7.741)	(-1.139, 6.842)
Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	0.59 (-5.42, 6.60)	
Percentage difference (pegcetacoplan vs placebo)	20.77	
p-value (pegcetacoplan vs placebo)	0.8445	
Based on Table 33, CS ¹ Note: Baseline is defined as the most recent non-missing measurement prior to taking the first dose of investigational product. Note: ANCOVA model includes treatment as fixed effect, adjusted for baseline EQ-5D-5L Score, disease type, and stratification factors.		

	Pegcetacoplan (N=63)	Placebo (N=61)
ANCOVA = analysis of covariance; CI = confidence interval; CS = company submission; EQ-5D-5L = European Quality of Life-5 Dimension-5 Levels; ITT = intention-to-treat; LS = least-square; SE = standard error		

EAG comment: The results from VALIANT generally show that the addition of pegcetacoplan to SoC improves all outcomes over the 26-week RCP. Most improvements were statistically significant, including the primary outcome, which is log-transformed ratio of uPCR at week 26 compared to baseline, and change in eGFR from baseline (least-square [LS] mean, 95% confidence interval [CI]), which is one of the key secondary outcomes.

3.2.5.5 Week 52 overall study (ITT set)

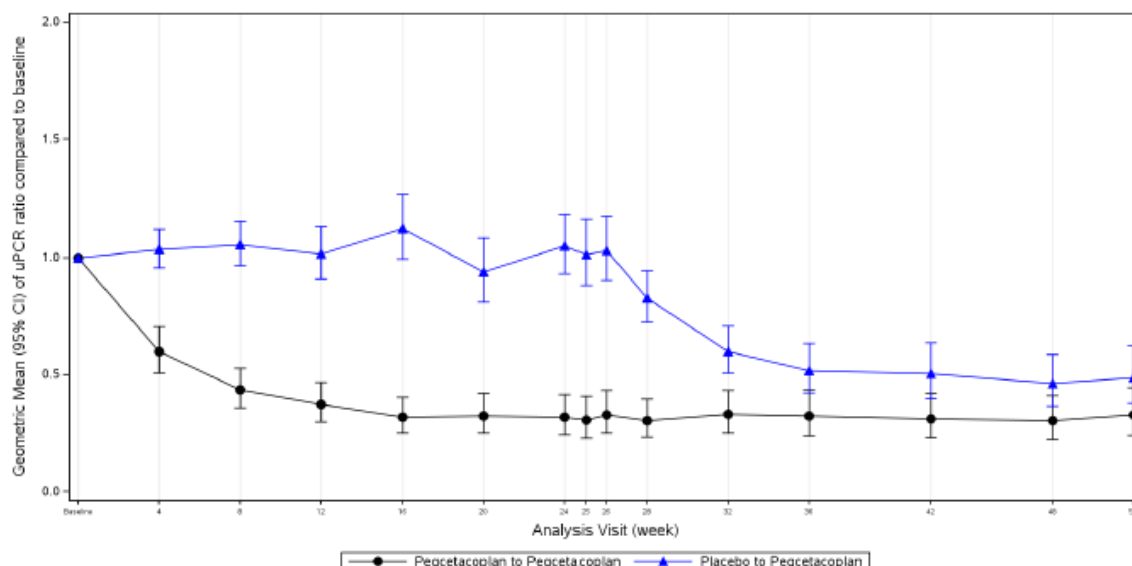
3.2.5.5.1 Difference in least-square means of log-transformed uPCR at week 52

This outcome is summarised in Table 3.35. and Figure 3.7.

Table 3.35: Analysis of CFB in log-transformed FMU uPCR (mg/g) with MMRM—overall study (ITT set)

Week	Parameter	Pegcetacoplan-to-pegcetacoplan (N=63)	Placebo-to-pegcetacoplan (N=61)
Week 52	Estimated/comparisons ^a		
	LS mean (SE)	−1.11 (0.15)	−0.72 (0.13)
	95% CI of LS mean	(−1.42 to −0.81)	(−0.97 to −0.47)
	Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	−0.39 (−0.79 to −0.00)	
	Geometric means (95% CI) ^b	0.33(0.24 to 0.44)	0.487 (0.379 to 0.625)
	Geometric means ratios (95% CI) (pegcetacoplan vs placebo) ^b	0.67 (0.45 to 0.99)	
Adapted from Table 34, CS¹ ^a An MMRM including fixed categorical effect for treatment group, visit, disease type, baseline immunosuppressants use, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline log-transformed uPCR was used to analyse the log-transformed ratio of uPCR compared to baseline. Missing data were imputed implicitly within the MMRM in a hypothetical strategy under the assumption of missing at random. ^b Geometric means and ratios were estimated by the exponentiated LS means and differences. Note: Baseline uPCR value was to be calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. CFB = change from baseline; CI = confidence interval; CS = company submission; FMU = first morning urine; ITT = intention-to-treat; LS = least-square; MMRM = mixed-effects model for repeated measures; uPCR = urinary protein to creatinine ratio			

Figure 3.7: Geometric mean (95% CI) plot of CFB in log-transformed FMU uPCR (mg/g) by analysis visit and treatment group from MMRM for overall study (ITT set)



Source: Figure 9, CS¹

Notes: Baseline uPCR value was calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. An MMRM including fixed categorical effect for treatment group, visit, disease type, baseline immunosuppressants use, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline log-transformed uPCR, was used to analyse the log-transformed ratio of uPCR compared to baseline. Missing data will be imputed implicitly within the MMRM in a hypothetical strategy under the assumption of missing at random. Geometric means are estimated by the exponentiated LS means.

CFB = change from baseline; CI = confidence interval; CS = company submission; ITT = intention-to-treat; FMU = first-morning urine; LS = least-square; MMRM = mixed-effects model for repeated measures; uPCR = urinary protein to creatinine ratio

3.2.5.5.2 Proportion of participants who met the criteria for achieving a composite renal endpoint at week 52

This outcome is shown in Table 3.36.

Table 3.36: Proportion of participants who met criteria for achieving a composite renal endpoint at week 52 by treatment group—overall study (ITT set)

Parameter	Pegcetacoplan-to-pegcetacoplan (N=63)	Placebo-to-pegcetacoplan (N=61)
Participants who achieved the composite renal endpoint, n (%)	24 (38.1)	22 (36.1)
Participants with stable or improved eGFR compared to baseline ($\leq 15\%$ reduction in eGFR), n (%)	39 (61.9)	42 (68.8)
Participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%)	32 (50.8)	25 (40.9)
Participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%)	32 (50.8)	25 (40.9)

Adapted from Tables 35 and 36, CS¹

Notes: Baseline eGFR value was calculated using the last non-missing assessment prior to first dose of study treatment. Baseline uPCR value was calculated as the average of the uPCR measurements from at least 6 of

Parameter	Pegcetacoplan-to-pegcetacoplan (N=63)	Placebo-to-pegcetacoplan (N=61)
the 9 FMU samples collected between the start of screening and day 1, inclusive. Participants who met criteria for achieving a composite renal endpoint were defined as: (1) a stable or improved eGFR compared to baseline ($\leq 15\%$ reduction in eGFR), and (2) a $\geq 50\%$ reduction in uPCR compared to baseline. A composite strategy was used where the composite renal endpoint status at or after the occurrence of any of the ICEs was regarded as non-responder. Participants with missing eGFR and/or uPCR values at week 52 for reasons other than ICEs were regarded as nonresponder. CS = company submission; eGFR = estimated glomerular filtration rate; FMU = first morning urine; ICE = intercurrent event; ITT = intention-to-treat; uPCR = urinary protein to creatinine ratio		

3.2.5.5.3 Change from baseline in eGFR at week 52

This outcome is shown in Table 3.37.

Table 3.37: Analysis of CFB in eGFR (mL/min/1.73 m²) with MMRM at week 52 for overall study (ITT set)

Parameter	Pegcetacoplan-to-pegcetacoplan (N=63)	Placebo-to-pegcetacoplan (N=61)
LS mean (SE)	-3.65 (2.66)	-4.72 (2.23)
95% CI of LS mean	(-8.93 to 1.62)	(-9.13 to -0.31)
Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	1.067 (-5.80 to 7.94)	
Percentage difference (pegcetacoplan vs placebo)	-22.6	
Source: Table 37, CS¹ Notes: An MMRM including fixed categorical effect for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline eGFR, was used to analyse the mean CFB in eGFR. Missing data were imputed implicitly within the MMRM in a hypothetical strategy under the assumption of missing at random. Baseline eGFR value was calculated using the last non-missing assessment prior to first dose of study treatment. CFB = change from baseline; CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; ITT = intention-to-treat; LS = least-square; MMRM = mixed-effects model for repeated measures; SE = standard error		

EAG comment: In the longer term, the magnitude of the primary outcome on pegcetacoplan seems to be maintained in the OLP i.e., after the RCP of 26 weeks. However, the magnitude of the outcome of those randomised to placebo also improved, although this is probably due to a switch to pegcetacoplan. However, there does appear to be a deterioration in other outcomes for those randomised to pegcetacoplan between 26 and 52 weeks, including for eGFR. Therefore, it might be that there could be a deterioration in the treatment effect between pegcetacoplan and placebo beyond 26 weeks, although there appear to be no data to test this given the switch to pegcetacoplan. This is therefore identified as a key issue and is also discussed in Section 3.2.7.

3.2.6 Subgroup analyses of VALIANT

3.2.6.1 Proteinuria and eGFR

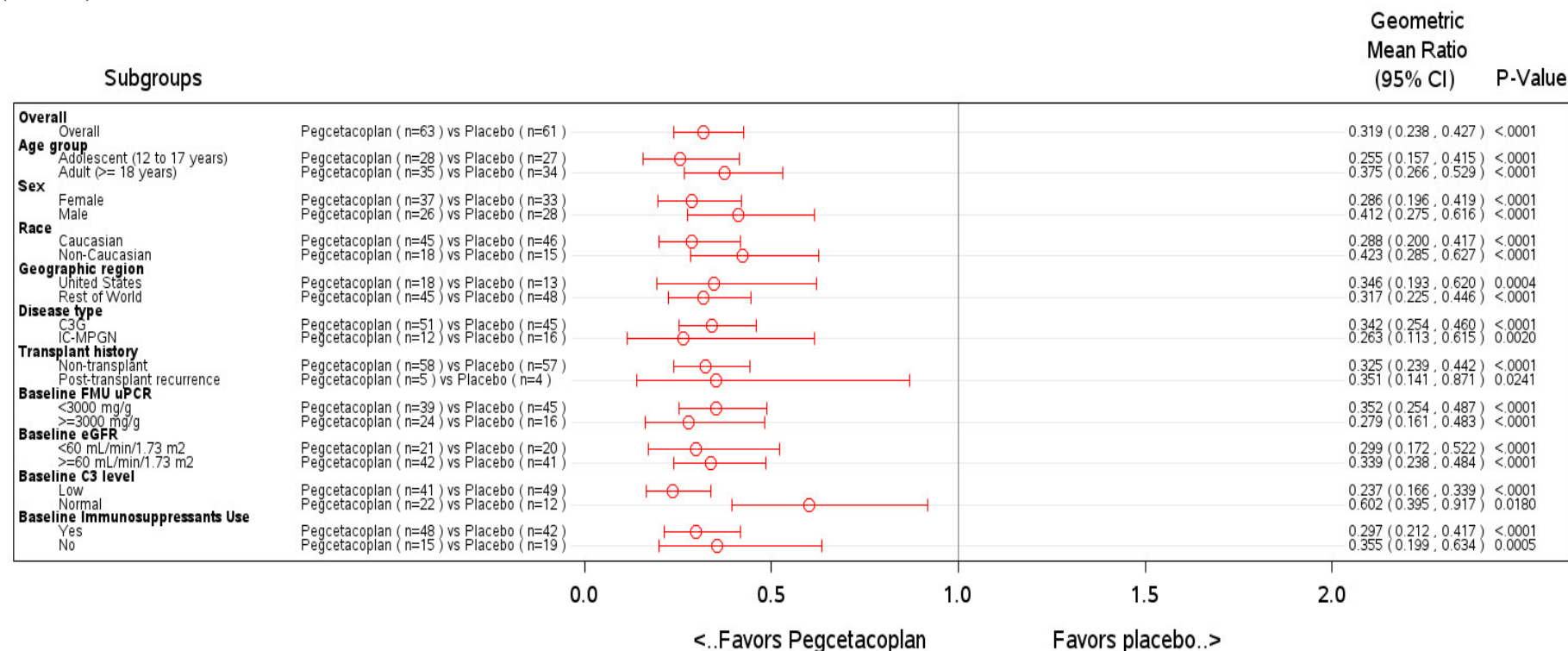
Subgroup analyses were reported for the primary outcome and key secondary outcomes.⁹ The results for two of these outcomes are shown in Figures 3.8 to 3.9.

3.2.6.2 Composite renal endpoint and proportion of participants with a reduction of $\geq 50\%$ from baseline uPCR

The statistically significant difference was maintained for two of the three subgroup analyses i.e., disease (C3G or IC-MPGN) and age (adolescents or adults). For transplant status, it was for non-transplant, but there were only three patients who had a transplant, none of which were in the placebo arm.

EAG comment: The results of the primary analyses seem not to be affected substantially by subgroup analysis in terms of disease, age or transplant status. The exception is C3 level where pegcetacoplan appears to be less effective in the normal subgroup for both proteinuria and eGFR. This means that baseline C3 level is a potential treatment effect modifier. Given that baseline C3 level is a potential treatment effect modifier, the company did not conduct relevant scenario analyses for the assessment of cost effectiveness. Therefore, there was uncertainty on the impact of this potential treatment effect modifier on the cost effectiveness assessment, which implies a key issue.

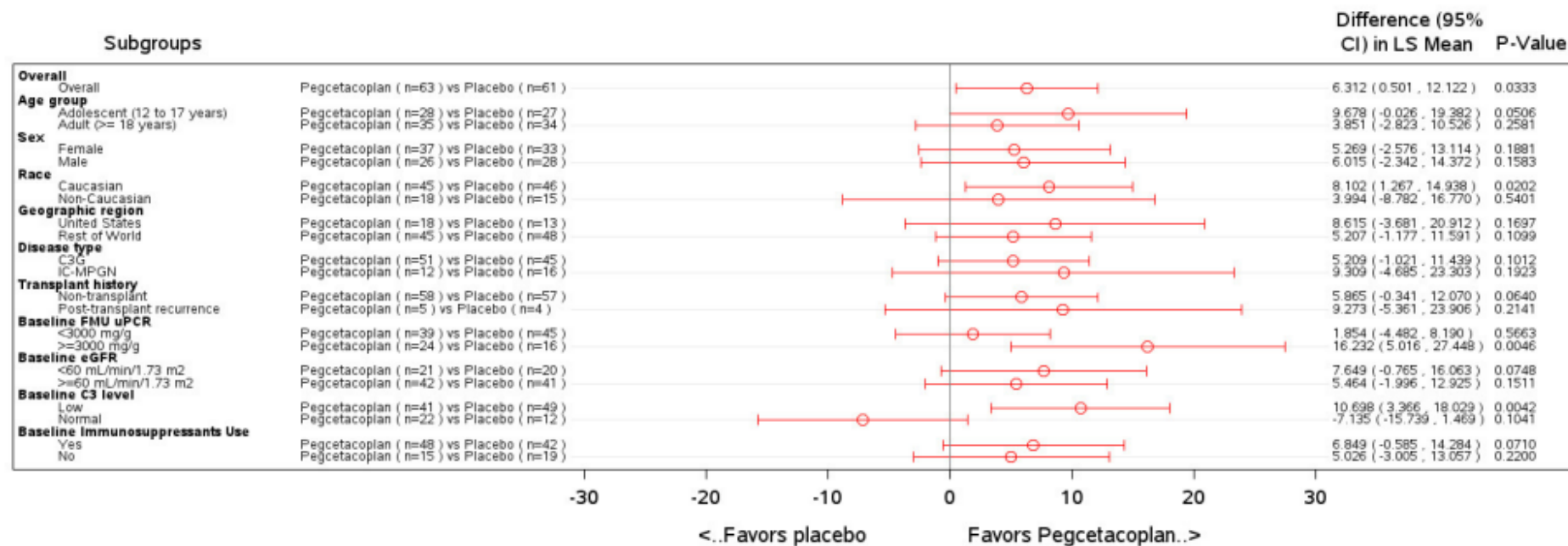
Figure 3.8: Geometric mean ratio (95% CI) of uPCR at week 26 compared to baseline by treatment group from MMRM by subgroups for RCP (ITT set)



Adapted from Figure 30, Appendix C⁹

Notes: An MMRM including fixed categorical effect for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline log-transformed uPCR, was utilised to analyse the log-transformed ratio of uPCR at week 26 compared to baseline. Use of prohibited medications or rescue therapies or start renal replacement therapy was handled by hypothetical strategy, discontinuation of treatment was handled by treatment policy strategy. The LS mean treatment difference at week 26 was estimated using a composite contrast of equal-weighted average over weeks 24, 25, and 26. Baseline uPCR value was calculated as the average of the uPCR measurements from at least 6 of the 9 first-morning spot urine samples collected between the start of screening and day 1, inclusive. C3G = C3 glomerulopathy; CI = confidence interval; eGFR = estimated glomerular filtration rate; FMU = first morning urine; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; ITT = intention-to-treat; LS = least-square; MMRM = mixed-effect model for repeated measures; RCP = randomised controlled period; uPCR = urinary protein to creatinine ratio

Figure 3.9: LS mean (95% CI) treatment difference at week 26 in the change from baseline in eGFR (mL/min/1.73 m²) by treatment group from MMRM by subgroups for RCP (ITT set)



Adapted from Figure 31, Appendix C⁹

Notes: An MMRM including fixed categorical effect for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline eGFR, is utilised to analyse the mean change from baseline to week 26 in eGFR. Use of prohibited medications or rescue therapies or start renal replacement therapy was handled by hypothetical strategy, discontinuation of treatment is handled by treatment policy strategy. Baseline eGFR value was calculated using the last non missing assessment prior to first dose.

CI = confidence interval; eGFR = estimated glomerular filtration rate; FMU = first morning urine; ITT = intention-to-treat; LS = least-square; MMRM = mixed-effect model for repeated measures; RCP = randomised controlled period; uPCR = urinary protein to creatinine ratio

3.2.7 VALE study clinical effectiveness

3.2.7.1.1 Primary efficacy outcome-Log-transformed ratio of uPCR over time

A summary of this outcome from the end of the randomised period (26 weeks) is provided in Table 3.38).

Table 3.38: Analysis of change from VALIANT baseline in geometric mean ratio of FMU UPCR (mg/g) with MMRM for select visits - combined analysis (VALIANT ITT set)

Analysis visit	Parameter	Pegcetacoplan to pegcetacoplan (N=63)	Placebo to pegcetacoplan (N=61)
Week 26	Estimates/comparisons ^a LS mean (SE) 95% CI of LS mean Difference (95% CI) in LS mean (pegcetacoplan vs pegcetacoplan) P value (pegcetacoplan – placebo) Geometric means (95% CI) ^b Geometric means ratio (95% CI) (pegcetacoplan vs placebo) ^b	-1.11 (0.13) -1.37 to -0.84 -1.13 (-1.42 to -0.83) < .0001 0.33 (0.25-0.43) 0.32 (0.24-0.44)	0.02 (0.07) -0.11 to 0.15 1.02 (0.89-1.16)
Week 36	Estimates/comparisons ^a LS mean (SE) 95% CI of LS mean Difference (95% CI) in LS mean (pegcetacoplan vs pegcetacoplan) P value (pegcetacoplan – placebo) Geometric means (95% CI) ^b Geometric means ratio (95% CI) (pegcetacoplan vs placebo) ^b	-1.07 (0.16) -1.38 to -0.76 -0.33 (-0.71 to 0.05) 0.0839 0.34 (0.25-0.46) 0.72 (0.49-1.05)	-0.74 (0.11) -0.95 to -0.5 0.48 (0.38-0.59)
Week 52	Estimates/comparisons ^a LS mean (SE) 95% CI of LS mean Difference (95% CI) in LS mean (pegcetacoplan vs pegcetacoplan) P value (pegcetacoplan – placebo) Geometric means (95% CI) ^b Geometric means ratio (95% CI) (pegcetacoplan vs placebo) ^b	-1.18 (0.17) -1.51 to -0.84 -0.29 (-0.77 to 0.17) 0.2135 0.31 (0.22-0.43) 0.74 (0.47-1.19)	-0.88 (0.17) -1.21 to -0.55 0.42 (0.29-0.58)
Week 76	Estimates/comparisons ^a LS mean (SE) 95% CI of LS mean Difference (95% CI) in LS mean (pegcetacoplan vs pegcetacoplan) P value (pegcetacoplan – placebo) Geometric means (95% CI) ^b Geometric means ratio (95% CI) (pegcetacoplan vs placebo) ^b	-1.16 (0.24) (-1.63, -0.68) -0.09 (-0.72, 0.52) 0.7544 0.32 (0.19, 0.51) 0.91 (0.49, 1.69)	-1.06 (0.20) (-1.46, -0.66) 0.35 (0.23, 0.52)

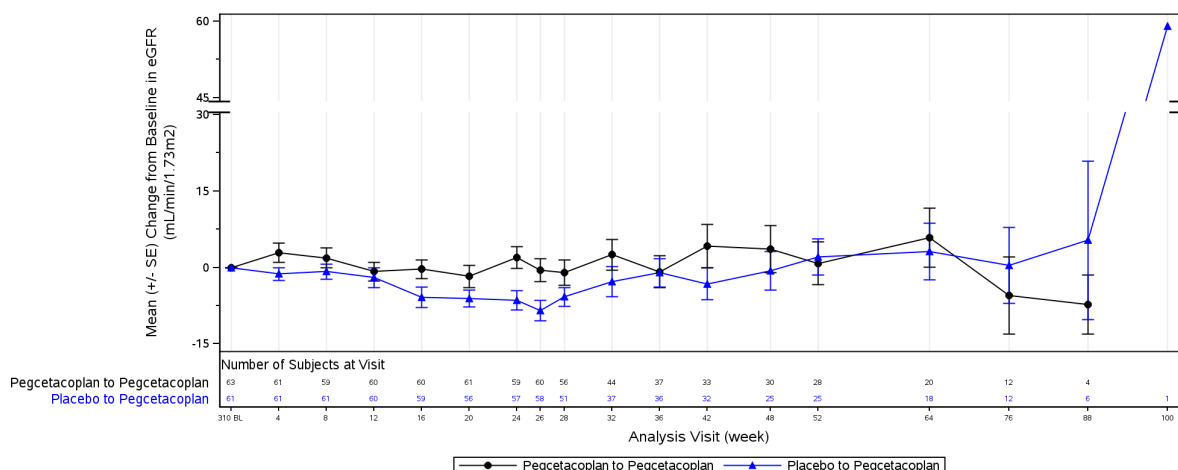
Analysis visit	Parameter	Pegcetacoplan to pegcetacoplan (N=63)	Placebo to pegcetacoplan (N=61)
Source: Table 38, CS ¹			
^a MMRM including the fixed categorical effect for treatment group, visit, disease type, baseline immunosuppressants use, stratification factors, and the visit-by-treatment group interactions as well as the continuous fixed covariate of baseline log-transformed ratio of uPCR, was utilised to analyse the geometric mean ratio of uPCR at each visit compared to the VALIANT baseline.			
^b Geometric means and ratios were estimated by exponentiated LS means and differences. Note: VALIANT study baseline: the baseline was defined as the baseline value used in the antecedent study (VALIANT) participant had enrolled in. Baseline uPCR value were calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive.			
CI = confidence interval; CS = company submission; FMU = first morning urine; ITT = intention-to-treat; LS = least-square; MMRM = mixed-effect model for repeated measures; n = number of evaluable participants; N = number of participants; SE = standard error; uPCR = urinary protein to creatinine ratio			

3.2.7.2 Secondary efficacy outcomes

3.2.7.2.1 eGFR change over time

See Figure 3.10 for the mean ($\pm$ SE) change in eGFR from baseline over time for participants randomised in VALIANT (ITT set). Based on the CS findings, Figure 14 indicated that:¹ “for the pegcetacoplan-to-pegcetacoplan group, mean eGFR was stable through to week 64; for the placebo-to-pegcetacoplan group, mean eGFR initially decreased through to week 26 while on placebo treatment, then stabilized or slightly increased after start of pegcetacoplan treatment”.

Figure 3.10: Mean ($\pm$ SE) change from VALIANT baseline of eGFR (mL/min/1.73 m²) by analysis visit and treatment group ITT set



Adapted from Figure 14, CS¹

Note: VALIANT study baseline: The eGFR baseline was defined as the baseline value used in the antecedent study (VALIANT) in which the participant had enrolled. Analysis visit week was counted after receiving the first dose of pegcetacoplan in the VALIANT Study.

CS = company submission; eGFR = estimated glomerular filtration rate; ITT = intention-to-treat; SE = standard error

3.2.7.2.2 Proportion of participants achieving at least 50% reduction in uPCR from the pre-treatment value over time

A summary of this outcome from week 4, through the end of the randomised period (26 weeks) is provided in Table 3.39).

Table 3.39: Analysis of the total participants achieving a reduction of at least 50% from re-aligned baseline in FMU uPCR (mg/g) - combined analysis VALE ITT set

Analysis visit ^a		Total (N=53)
Week 4	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%) 95% CI of proportion	52 21 (40.4) 27.01-54.90
Week 12	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%) 95% CI of proportion	45 29 (64.4) 48.78-78.13
Week 20	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%) 95% CI of proportion	46 31 (67.4) 51.98-80.47
Week 26	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%) 95% CI of proportion	45 32 (71.1) 55.69-83.63
Week 36	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%) 95% CI of proportion	42 28 (66.7) 50.45- 80.43
Week 48	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%) 95% CI of proportion	37 25 (66.7) 50.21-81.99
Week 64	Number of evaluable participants, n Proportion of participants with $\geq 50\%$ reduction in uPCR compared to baseline, n (%) 95% CI of proportion	26 15 (57.7) 36.92-76.65
Adapted from Table 39, CS ¹ ^a Analysis visits were based on re-aligned baseline. The visit week were counted after receiving the first dose of pegcetacoplan in VALIANT. Notes: The 2-sided 95% CI for proportion of responders was calculated using the Clopper-Pearson method. Re-Aligned baseline: For participants who received pegcetacoplan during the randomised controlled period (RCP) in VALIANT, the baseline was defined as the baseline value used in VALIANT, i.e., the average of the UPCR values from the FMU samples collected during screening and on day 1 before dosing in that study. For participants who received placebo during the RCP in the antecedent study, the baseline was defined as the last available non-missing assessment prior to enrolling into the open-label period (OLP) in VALIANT, i.e., baseline was calculated as the average of the UPCR values from the FMU samples collected during week 24, week 25, and week 26 (or, the 3 most recent visits prior to the first administration of pegcetacoplan) in that study. CI = confidence interval; FMU = first morning urine; ITT = intention-to-treat; n = number of evaluable participants; N = number of participants; uPCR = urinary protein to creatinine ratio		

3.2.7.2.3 Proportion of participants with stable or improved eGFR values over time

A summary of this outcome from week 4, and through the end of the randomised period (26 weeks) is provided in Table 3.40).

Table 3.40: Analysis of the total participants with eGFR (mL/min/1.73 m²) values that are stable or improved from re-aligned baseline - combined analysis - VALE ITT set

Analysis visit ^a		Total (N=53)
Week 4	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	52 50 (96.2) 86.79-99.53
Week 12	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	43 38 (88.4) 74.92-96.11
Week 20	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	37 32 (86.5) 71.23-95.46
Week 26	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	40 34 (85.0) 70.16-94.29
Week 36	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	39 30 (76.9) 60.67-88.87
Week 48	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	34 23 (67.6) 49.47-82.61
Week 64	Number of evaluable participants, n Participants with stable or improved eGFR from baseline, n (%) 95% CI of proportion	26 21 (80.8) 60.65-93.45
Adapted from Table 40, CS ¹ ^a Analysis visits are based on re-aligned baseline. The visit week is counted after receiving the first dose of pegcetacoplan in VALIANT study. Notes: The 2-sided 95% CI for proportion of responders is calculated using the Clopper-Pearson method. Re-aligned baseline: For participants who received pegcetacoplan during the randomised controlled period (RCP) in VALIANT, the baseline was defined as the baseline value used in VALIANT. For participants who received placebo during the RCP in the antecedent study, the baseline was defined as the last available non-missing assessment prior to enrolling into the (OLP) in VALIANT. CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; n = number of evaluable participants; N = number of participants; OLP = open-label period; RCP = randomised controlled period		

3.2.7.2.4 Proportion of participants with proteinuria <1g/day over time

A summary of this outcome from week 12, and through the end of the randomised period (26 weeks) is provided in Table 3.41.

Table 3.41: Analysis of the total participants with proteinuria < 1g/day based on re-aligned baseline – combined analysis (VALE ITT set)

Analysis visit ^a		Total (N=53)
Week 12	Number of evaluable participants, n Participants achieving proteinuria < 1g/day, n (%) 95% CI of proportion	49 22 (44.9) 30.67-59.77
Week 24	Number of evaluable participants, n Participants achieving proteinuria < 1g/day, n (%) 95% CI of proportion	51 25 (49.0) 34.75-63.40
Week 36	Number of evaluable participants, n Participants achieving proteinuria < 1g/day, n (%) 95% CI of proportion	26 10 (38.5) 20.23-59.43
Week 48	Number of evaluable participants, n Participants achieving proteinuria < 1g/day, n (%) 95% CI of proportion	26 14 (53.8) 33.37-73.41
Adapted from Table 41, CS ¹ ^a Analysis visits were based on re-aligned baseline. The visit week was counted after receiving the first dose of pegcetacoplan in VALIANT. Note: The 2-sided 95% CI for proportion of responders was calculated using the Clopper-Pearson method. CI = confidence interval; CS = company submission; ITT = intention-to-treat; n = number of evaluable participants; N = number of participants		

3.2.7.2.5 The change from pretreatment in the FACIT-Fatigue Scale score

The CS stated that there was no observed significant changes in FACIT-Fatigue Scale score for the total group.¹ According to the company, this may have been attributed to the small sample size.

3.2.7.2.6 Time to progression to a composite clinical outcome (at least one of the following: sustained doubling of serum creatinine, progression to chronic kidney disease stage 5 or ESRD, renal transplantation, or death from renal or cardiovascular disease)

The company stated that:¹ “number of participants with events was too low to estimate median time to event. There was a total of 6 (5.0%) participants who met composite clinical outcome with pegcetacoplan up to 21 months.”

3.2.7.2.7 HRQoL Assessments

Similarly for this outcome, the CS stated that due to the small sample sizes no meaningful summaries have been produced.¹

EAG comment: The results from VALE generally show that the magnitude of the primary outcome observed for pegcetacoplan plus SoC over the 26-week RCP is sustained, including the primary outcome up to 76 weeks. Also, switching from SoC only results in an improvement that almost matched the outcome with pegcetacoplan plus SoC. However, the analysis that showed this was based on the VALIANT ITT set, which included all patients in VALIANT, and not only the 53 participants who were enrolled in VALE. Nevertheless, analysis of the VALE ITT set, i.e., only those 53 patients showed a similar sustained magnitude of the primary outcome at 64 weeks.

3.2.8 Adverse reactions

3.2.8.1 VALIANT adverse events

There was one death because of respiratory failure due to COVID-19 pneumonia in the pegcetacoplan group which was considered not to be related to study treatment.¹ Additionally, no serious cases of infection by encapsulated bacteria were reported during the RCP. A summary of these adverse events during the randomised period (26 weeks) is provided in Table 3.42).

Table 3.42: Overview of adverse events during the RCP (safety set)

Characteristics	Pegcetacoplan (N=63), n (%) m	Placebo (N=61), n (%) m	Overall (N = 124), n (%) m
Any TEAE	53 (84.1) 390	57 (93.4) 380	110 (88.7) 770
Treatment-related TEAE	25 (39.7) 125	26 (42.6) 134	51 (41.1) 259
Infusion-related TEAEs	21 (33.3) 110	16 (26.2) 124	37 (29.8) 234
Serious TEAE	6 (9.5) 9	6 (9.8) 10	12 (9.7) 19
Maximum severity of TEAEs			
Mild	27 (42.9)	26 (42.6)	53 (42.7)
Moderate	23 (36.5)	27 (44.3)	50 (40.3)
Severe	3 (4.8)	4 (6.6)	7 (5.6)
Infusion site reaction	18 (28.6) 103	17 (27.9) 121	35 (28.2) 224
TEAE leading to treatment withdrawn	2 (3.2) 2	2 (3.3) 2	4 (3.2) 4
TEAE leading to dose interruption	7 (11.1) 13	12 (19.7) 29	19 (15.3) 42
TEAE leading to study discontinuation	1 (1.6) 1	1 (1.6) 1	2 (1.6) 2
TEAE leading to death	1 (1.6) 1	0	1 (0.8) 1
Rejection episodes	0	0	0
Graft loss	0		

Adapted from Table 49, CS.¹

Notes: A TEAE was defined as any new adverse event that began, or any pre-existing condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences were counted in the total events count. A treatment-related AE was defined as a TEAE with a relationship to study drug or definitely related or possibly related. Any AEs with missing or unknown relationship was considered as related to study drug. Rejection episodes and graft loss were summarised for post-transplant participant only. Percentage will be based on post-transplant participant.

CS = company submission; m = number of events; n = number of participants; TEAE = treatment-emergent adverse event

3.2.8.1.1 Commonly reported AEs

A summary of this commonly reported AEs during the randomised period (26 weeks) is provided in Table 3.43).

Table 3.43: Summary of common TEAEs (experienced by ≥ 3 participants in either treatment group) during the RCP (safety set)

System Organ Class Preferred Term	Pegcetacoplan (N=63)	Placebo (N=61)
Any TEAE n (%) m	53 (84.1) 390	57 (93.4) 380
Infections and infestations, n (%)	35 (55.6)	27 (44.3)
Nasopharyngitis	11 (17.5)	7 (11.5)
Influenza	7 (11.1)	3 (4.9)
Upper respiratory tract infection	4 (6.3)	5 (8.2)
COVID-19	2 (3.2)	4 (6.6)
Gastroenteritis	2 (3.2)	3 (4.9)
Herpes zoster	0	3 (4.9)
General disorders and administration site conditions, n (%)	29 (46.0)	29 (47.5)
Pyrexia	12 (19.0)	6 (9.8)
Fatigue	4 (6.3)	1 (1.6)
Infusion site erythema	3 (4.8)	0
Injection site pruritus	3 (4.8)	1 (1.6)
Oedema	3 (4.8)	5 (8.2)
Oedema peripheral	3 (4.8)	3 (4.9)
Injection site pain	2 (3.2)	5 (8.2)
Injection site swelling	2 (3.2)	6 (9.8)
Asthenia	0	3 (4.9)
Infusion site pain	0	3 (4.9)
Gastrointestinal disorders, n (%)	19 (30.2)	17 (27.9)
Nausea	6 (9.5)	4 (6.6)
Vomiting	5 (7.9)	8 (13.1)
Abdominal pain	4 (6.3)	4 (6.6)
Abdominal pain upper	3 (4.8)	2 (3.3)
Dyspepsia	3 (4.8)	0
Diarrhoea	2 (3.2)	7 (11.5)
Respiratory, thoracic and mediastinal disorders, n (%)	12 (19.0)	9 (14.8)
Cough	6 (9.5)	1 (1.6)
Oropharyngeal pain	3 (4.8)	3 (4.9)
Rhinorrhoea	3 (4.8)	2 (3.3)
Skin and subcutaneous tissue disorders, n (%)	12 (19.0)	10 (16.4)
Acne	0	4 (6.6)
Nervous system disorders, n (%)	10 (15.9)	13 (21.3)
Headache	8 (12.7)	10 (16.4)
Dizziness	0	6 (9.8)
Injury, poisoning and procedural complications, n (%)	8 (12.7)	7 (11.5)
Contusion	5 (7.9)	2 (3.3)
Investigations	8 (12.7)	13 (21.3)
Blood creatine phosphokinase increased	3 (4.8)	2 (3.3)
Blood cholesterol increased	0	3 (4.9)
Musculoskeletal and connective tissue disorders, n (%)	8 (12.7)	8 (13.1)
Muscle spasms	0	3 (4.9)

System Organ Class Preferred Term	Pegcetacoplan (N=63)	Placebo (N=61)
Renal and urinary disorders, n (%)	7 (11.1)	12 (19.7)
Acute kidney injury	4 (6.3)	2 (3.3)
Vascular disorders, n (%)	7 (11.1)	5 (8.2)
Hypertension	4 (6.3)	5 (8.2)
Blood and lymphatic system disorders, N (%)	5 (7.9)	7 (11.5)
Anaemia	0	4 (6.6)
Source: Table 50, CS ¹ Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n), and all occurrences were counted in the total events count (m). Adverse events were coded to SOC and PT using MedDRA Version 26.0 CS = company submission; n = number of participants; PT = Preferred Term; RCP = randomised controlled period; SOC = System Organ Class; TEAE= treatment-emergent adverse event		

3.2.8.1.2 Treatment-related AEs

A summary of this commonly reported treatment-related AEs during the randomised period (26 weeks) is provided in Table 3.44).

Table 3.44: Treatment-related AEs (experienced by ≥ 3 participants) in either treatment group) during the RCP (safety set)

System Organ Class Preferred Term	Pegcetacoplan (N=63), n (%)	Placebo (N=61), n (%)
Any TEAE, n (%), m	25 (39.7) 125	26 (42.6) 134
General disorders and site conditions	18 (28.6)	13 (21.3)
Pyrexia	4 (6.3)	0
Injection site pruritus	3 (4.8)	1 (1.6)
Injection site pain	2 (3.2)	5 (8.2)
Injection site swelling	2 (3.2)	4 (6.6)
Infusion site pain	0	3 (4.9)
Nervous system disorders	3 (4.8)	4 (6.6)
Headache	3 (4.8)	3 (4.9)
Source: Table 51, CS ¹ Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n), and all occurrences were counted in the total events count (m). Adverse events were coded to SOC and PT using MedDRA Version 26.0. CS = company submission; m = number of events; n = number of participants; PT = Preferred Term; RCP = randomised controlled period; SOC = System Organ Class; TEAE = treatment-emergent adverse event		

3.2.8.1.3 Deaths, serious adverse events (SAEs) and other significant AEs

A summary of serious TEAEs during the randomised period (26 weeks) is provided in Table 3.45.

Table 3.45: Serious TEAEs during the RCP (safety set)

System Organ Class Preferred Term	Pegcetacoplan, N=63, n (%)	Placebo, N=61, n (%)
Any serious TEAEs, n (%), m	6 (9.5) 9	6 (9.8) 10
Infections and infestations, n (%)	3 (4.8)	1 (1.6)
COVID-19 pneumonia	1 (1.6)	0
Influenza	1 (1.6)	0
Pneumonia	1 (1.6)	0
Viral infection	0	1 (1.6)
Renal and urinary disorders, n (%)	2 (3.2)	4 (6.6)
Acute kidney injury	1 (1.6)	2 (3.3)
Nephrotic syndrome	1 (1.6)	0
Proteinuria	0	1 (1.6)
Tubulointerstitial nephritis	0	1 (1.6)
General disorders and administration site conditions, n (%)	1 (1.6)	0
Pyrexia	1 (1.6)	0
Respiratory, thoracic and mediastinal disorders, n (%)	1 (1.6)	0
Respiratory failure	1 (1.6)	0
Vascular disorders	1 (1.6)	0
Hypertension	1 (1.6)	0
Gastrointestinal disorders	0	1 (1.6)
Vomiting	0	1 (1.6)
Investigations, n (%)	0	1 (1.6)
Blood creatinine increased	0	1 (1.6)
Pregnancy, puerperium and perinatal conditions	0	1 (1.6)
Abortion spontaneous	0	1 (1.6)
Pregnancy	0	1 (1.6)
Source: Table 54, CS ¹		
Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n), and all occurrences were counted in the total events count (m). Adverse events were coded to SOC and PT using MedDRA Version 26.0.		
CS = company submission; n = number of participants; PT = Preferred Term; RCP = randomised controlled period; SOC = System Organ Class; TEAE= treatment-emergent adverse event		

3.2.8.2 VALE adverse events

An overall summary of AEs is provided in Table 3.46.

Table 3.46: Overall summary of TEAEs – combined analysis (re-aligned safety set)

Events		VALIANT ^e (N=120)	VALE ^f (N=53)	Combined (N=120)
All TEAEs ^{a,b}	Number of participants, n (%)	91 (75.8)	30 (56.6)	94 (78.3)
	Total events, n	726	125	851
	Unique events, n	467	66	522
Pegcetacoplan-related TEAE ^c	Number of participants, n (%)	44 (36.7)	10 (18.9)	49 (40.8)
	Total events, n	271	70	341
	Unique events, n	94	14	105
Infusion-related TEAEs	Number of participants, n (%)	34 (28.3)	6 (11.3)	37 (30.8)
	Total events, n	226	65	291
	Unique events, n	56	10	63
Serious TEAE	Number of participants, n (%)	11 (9.2)	1 (1.9)	12 (10.0)
	Total events, n	23	2	25
	Unique events, n	20	2	22
Maximum severity of TEAEs	Mild, n (%)	47 (39.2)	19 (35.8)	45 (37.5)
	Moderate	36 (30.0)	10 (18.9)	40 (33.3)
	Severe	8 (6.7)	1 (1.9)	9 (7.5)
Infusion site reaction	Number of participants, n (%)	32 (26.7)	6 (11.3)	35 (29.2)
	Total events, n	227	65	292
	Unique events, n	52	10	59
TEAE leading to treatment withdrawn	Number of participants, n (%)	4 (3.3)	1 (1.9)	5 (4.2)
	Total events, n	4	1	5
	Unique events, n	4	1	5
TEAE leading to dose interruption	Number of participants, n (%)	17 (14.2)	0	17 (14.2)
	Total events, n	33	0	33
	Unique events, n	33	0	33
TEAE leading to study discontinuation	Number of participants, n (%)	2 (1.7)	0	2 (1.7)
	Total events, n	2	0	2
	Unique events, n	2	0	2
TEAE leading to death	Number of participants, n (%)	1 (0.8)	0	1 (0.8)
Rejection episodes ^d	Number of participants, n (%)	0	0	0
	Total events, n	0	0	0
Graft loss ^d	Number of participants, n (%)	0	0	0

Events		VALIANT ^e (N=120)	VALE ^f (N=53)	Combined (N=120)
	Total events, n	0	0	0
Source: Table 55, CS ¹ ^a TEAEs were defined as any new AEs that began, or any pre-existing condition that worsened in severity, after the first ever dose of study medication in either VALIANT or VALE and up to 56 days beyond the last dose of study drug. ^b If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences are counted in the total events count. ^c A treatment-related AE was defined as a TEAE with a relationship to study drug of Definitely Related or Possibly Related. Any AEs with missing or unknown relationship were considered as related to study drug. ^d Rejection episodes and graft loss were summarised for post-transplant patients only. Percentages were based on post-transplant population. ^e Only TEAEs that occur in VALIANT and after the first dose of pegcetacoplan are summarised. ^f Only TEAEs that occur after the first dose of pegcetacoplan in VALE are summarised. AE = adverse event; CS = company submission; n = number of evaluable participants; N = number of participants; TEAE = treatment-emergent adverse event				

There were no deaths during pegcetacoplan treatment in VALE.

3.2.8.2.1 Exposure-adjusted incidence of TEAEs

Table 3.47 summarised the exposure-adjusted incidence of TEAEs for the participants. Overall, exposure-adjusted incidences between the two studies did not show an increase.¹

Table 3.47: Exposure-adjusted incidence summary of TEAEs- combined analysis (re-aligned safety set)

	VALIANT ^d (N=120)		VALE ^d (N=120)		Combined (N=120)	
Events	EY	n (e)	EY	n (e)	EY	n (e)
All TEAEs ^{a,b}	24.6	91 (370.4)	15.5	30 (193.2)	27.3	94 (344.0)
Treatment-related TEAE ^c	57.7	44 (76.2)	24.5	10 (40.8)	70.7	49 (69.3)
Infusion-related TEAEs	63.5	34 (53.5)	26.1	6 (23.0)	77.9	37 (47.5)
Serious TEAE	78.4	11 (14.0)	28.8	1 (3.5)	98.1	12 (12.2)
Maximum severity of TEAEs						
Mild	56.5	47 (83.2)	21.5	19 (88.4)	72.7	45 (61.9)
Moderate	63.0	36 (57.1)	25.1	10 (39.9)	76.7	40 (52.2)
Severe	80.5	8 (9.9)	28.8	1 (3.5)	101.3	9 (8.9)
Infusion site reaction	65.	32 (48.7)	26.1	6 (23.0)	82.9	35 (42.2)
TEAE leading to treatment withdrawn	83.3	4 (4.8)	29.2	1 (3.4)	105.3	5 (4.7)
TEAE leading to dose interruption	75.8	17 (22.4)	29.3	0	95.9	17 (17.7)
TEAE leading to study discontinuation	84.0	2 (2.4)	29.3	0	106.5	2 (1.9)
TEAE leading to death	84.2	1 (1.2)	29.3	0	106.7	1 (0.9)
Rejection episodes ^d	84.4	0	29.3	0	106.9	0
Graft loss ^d	84.4	0	29.3	0	106.9	0
Adapted from Table 56, CS ¹						

	VALIANT^d (N=120)	VALE^d (N=120)	Combined (N=120)
^a TEAEs were defined as any new AEs that began, or any pre-existing condition that worsened in severity, after the first ever dose of study medication in either Study APL2-C3G-310 or Study APL2-C3G-314 and up to 56 days beyond the last dose of study drug. ^b If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences were counted in the total events count. ^c A treatment-related AE was defined as a TEAE with a relationship to study drug of Definitely Related or Possibly Related. Any AEs with missing or unknown relationship were considered as related to study drug. ^d Rejection episodes and graft loss were summarised for post-transplant patients only. Percentages were based on post-transplant patient population. AE = adverse event; CS = company submission; e = number of events; EY = exposure years; n = number of evaluable participants; N = number of participants; TEAE = treatment-emergent adverse event			

3.2.8.2.2 Commonly reported AEs

A summary of this commonly reported AEs is provided in Table 3.48.

Table 3.48: TEAEs experienced by ≥5% of participants by System Organ Class and Preferred Term - combined analysis (re-aligned safety set)

System Organ Class Preferred Term	Combined (N=120)
Any TEAE, n (%)	94 (78.3)
General disorders and administration site conditions, n (%)	43 (35.8)
Pyrexia	16 (13.3)
Fatigue	7 (5.8)
Injection site erythema	6 (5.0)
Injection site swelling	6 (5.0)
Injection site pruritus	5 (4.2)
Infections and infestations, n (%)	56 (46.7)
Nasopharyngitis	15 (12.5)
Influenza	10 (8.3)
Upper respiratory tract infection	9 (7.5)
COVID-19	6 (5.0)
Bronchitis	5 (4.2)
Skin and subcutaneous tissue disorders, n (%)	29 (24.2)
Pruritus	8 (6.7)
Gastrointestinal disorders, n (%)	34 (28.3)
Diarrhoea	11 (9.2)
Nausea	9 (7.5)
Vomiting	9 (7.5)
Abdominal pain	7 (5.8)
Abdominal pain upper	5 (4.2)
Nervous system disorders, n (%)	16 (13.3)
Headache	11 (9.2)
Renal and urinary disorders, n (%)	16 (13.3)
Acute kidney injury	7 (5.8)
Vascular disorders, n (%)	16 (13.3)

System Organ Class Preferred Term	Combined (N=120)
Hypertension	8 (6.7)
Hypotension	6 (5.0)
Injury, poisoning and procedural complications, n (%)	15 (12.5)
Blood and lymphatic system disorders, n (%)	13 (10.8)
Respiratory, thoracic and mediastinal disorders, n (%)	20 (16.7)
Cough	8 (6.7)
Oropharyngeal pain	7 (5.8)
Metabolism and nutrition disorders, n (%)	19 (15.8)
Adapted from Table 57, CS ¹ CS = company submission; n = number of evaluable participants; N = number of participants; TEAE = treatment-emergent adverse event	

3.2.8.2.3 Infusion-related TEAEs

The company stated that in both studies, “the most frequently occurring infusion-related TEAEs included the following PTs: injection site erythema (occurring in 6 [5.0%] participants), injection site swelling (6 [5.0%] participants), injection site pruritus (5 [4.2%] participants), infusion site swelling (4 [3.3%] participants), and infusion site erythema, infusion site pruritus, and injection site reaction (all occurring in 3 [2.5%] participants).”

3.2.8.2.4 Deaths, SAEs and other significant AEs

One (0.8%) death was reported during the VALIANT study. Cause of death was respiratory failure (due to COVID-19 pneumonia), assessed as not related to study drug by the investigator/sponsor. No deaths were reported during VALE. Serious TEAEs are shown in Table 3.49.

Table 3.49: Serious TEAEs by System Organ Class and Preferred Term – combined analysis (re-aligned safety set)

Preferred Term	Combined (N=120)
Any TEAE, ^{a,b} n (%) m	12 (10.0) 25
Infections and infestations	5 (4.2)
COVID-19 pneumonia	1 (0.8)
Herpes zoster meningoencephalitis	1 (0.8)
Influenza	1 (0.8)
Pneumonia	1 (0.8)
Pneumonia streptococcal	1 (0.8)
Viral infection	1 (0.8)
Renal and urinary disorders	3 (2.5)
Acute kidney injury	2 (1.7)
End stage renal disease	1 (0.8)
Nephrotic syndrome	1 (0.8)
Renal impairment	1 (0.8)
General disorders and administration site conditions	2 (1.7)
Pyrexia	2 (1.7)

Preferred Term	Combined (N=120)
Injury, poisoning and procedural complications	2 (1.7)
Post procedural haematoma	1 (0.8)
Shunt malfunction	1 (0.8)
Metabolism and nutrition disorders	2 (1.7)
Dehydration	2 (1.7)
Hypoalbuminaemia	1 (0.8)
Vascular disorders	2 (1.7)
Hypertension	1 (0.8)
Hypertensive urgency	1 (0.8)
Gastrointestinal disorders	1 (0.8)
Vomiting	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.8)
Respiratory failure	1 (0.8)
Source: Table 59, CS ¹ ^a TEAEs were defined as any new AEs that began, or any pre-existing condition that worsened in severity, after the first ever dose of study medication in either VALIANT or VALE and up to 56 days beyond the last dose of study drug. ^b If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n), and all occurrences were counted in the total events count (m). Note: AEs were coded to SOC and PT using MedDRA Version 26.0. AE = adverse event; CS = company submission; n = number of evaluable participants; N = number of participants; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event	

EAG comment: The EAG did not have major concerns about the adverse events associated with pegcetacoplan treatment. One (0.8%) death, which was due to respiratory failure (due to COVID-19 pneumonia), was reported during the trial period of VALIANT. This death was assessed as not related to the study drug by the investigator/sponsor. No deaths were reported during the trial period of VALE. There were generally similar proportions of patients who experienced serious treatment-related adverse events between the pegcetacoplan treatment arm (9.5%) and the placebo arm (9.8%) during the randomised period (26 weeks) of the VALIANT trial. Only 1.9% of patients who experienced serious treatment-related adverse events were reported during the trial period of VALE.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The data of indirect treatment comparison from the CS were based on seven relevant studies being identified from the SLR.¹ Table 3.50 below presents a summary of the trials.

Table 3.50: Summary of trials included in the SLR

Study Name	Intervention/comparator	Disease
NOBLE (NCT04572854)	Pegcetacoplan vs SoC	Recurrent C3G and IC-MPGN
DISCOVERY (NCT03453619)	Pegcetacoplan	Native C3G
VALIANT (NCT05067127)	Pegcetacoplan vs placebo	Native and recurrent C3G and IC-MPGN

Study Name	Intervention/comparator	Disease
NCT038321146	Iptacopan	Native and recurrent C3G
NCT03955445 (extension of NCT03832114)	Iptacopan	Native and recurrent C3G
APPEAR-C3G (NCT04817618)	Iptacopan vs placebo + SoC	Native C3G
Pooled iptacopan analysis	Iptacopan	Native C3G
Based on Table 43 of CS ¹ ^a Recurrent disease is defined as C3G/IC-MPGN after kidney transplant and native disease is defined as C3G/IC-MPGN that is not recurrent. C3G = complement 3 glomerulopathy; CS = company submission; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; SLR = systematic literature review; SoC = standard of care		

Two studies (see Table 3.51) were evaluated for heterogeneity in terms of outcome definitions and timepoints.

Table 3.51: Summary of trials used to carry out the indirect treatment comparison

Study Name	Pegcetacoplan	Placebo	Iptacopan
VALIANT (NCT05067127)	Yes	Yes	No
APPEAR-C3G (NCT04817618)	No	Yes	Yes
Based on Table 44 of CS ¹ C3G = complement 3 glomerulopathy; CS = company submission			

The company compared the definition of outcomes for each of the studies. The following six outcomes were found to be consistent across both trials:¹

- Log-transformed ratio of uPCR compared to baseline
- Proportion of participants achieving composite renal endpoint
- Proportion of participants with at least 50% reduction in uPCR
- Change from baseline in activity score of the histologic index
- Change from baseline in eGFR
- Change from baseline in patient-reported fatigue (FACIT score).

The company stated that, although minor discrepancies in the definitions of these outcomes were noted between the VALIANT and APPEAR-C3G trials, the definitions were considered sufficiently consistent to conduct the indirect treatment comparison between pegcetacoplan and iptacopan. In both studies, the primary outcome was the percent change from baseline in log transformed uPCR, which was measured as FMU in VALIANT and 24-hour urine in the APPEAR C3G trial. In both clinical trials, the primary outcome was assessed with the mixed models for repeated measures (MMRM) model by using data with multiple imputations.¹

EAG comment: There seems to have been no explanation as to why only two trials were chosen for the ITC from the original six included in the SLR. It is reasonable to have chosen only RCTs for the ITC, but there appeared to be no formal assessment of eligibility or heterogeneity. Therefore, the EAG ask for clarification on two matters related to this:

1) Why NOBLE was excluded, to which the company responded that it was this was:³ “...*due to several key differences from VALIANT and APPEAR-C3G.*” These are:

- Population mismatch: NOBLE only post-transplant and APPEAR-C3G only native disease.

The EAG consider that this might not be considered so serious a problem given that the population of VALIANT, which is included in the ITC, is mixed, and a subgroup analysis for the primary endpoint and key secondary endpoints show little difference in treatment effect, which is what the company also concludes. However, the number of patients post-transplant in VALIANT was very small (n=9 vs 115), and the point estimates for all outcomes favoured pegcetacoplan more than in the non-transplant group.

- Sample size (n=13, only 3 of which are in the SoC group) too small for “...*reliable statistical inference and insufficient to conduct an MMRM analysis, consistent with the statistical method used in both VALIANT and APPEAR C3G.*”

No explicit justification was provided for the use of MMRM analysis, but the EAG note that there is evidence that this approach is less biased than last observation carried forward (LOCF) for imputing missing data when there are repeated measures for the same participant. However, it is unclear how this small sample might affect the reliability of the method, and so the EAG would not rule out the use of NOBLE only on that basis.

- Differences in design, NOBLE having been open-label and unblinded, and with a different primary endpoint, i.e., histology (change in C3c staining).
- Shorter follow-up (12 weeks, instead for approximately 6 months) for VALIANT.

The EAG agrees that these are all important sources of heterogeneity, which would limit inference if NOBLE was in the ITC. Therefore, although there might be some value in a scenario analysis, the exclusion of NOBLE is warranted. Indeed, the difference in population might actually be an argument for excluding the transplant patients from VALIANT to produce a pure non-transplant ITC. However, the number of patients that would be excluded and the difference in point estimates are small enough that the EAG considers that there would be little effect on the ITC results. Nevertheless, the EAG identify the potential heterogeneity in the trials of the ITC as a key issue, given the need to apply some judgement in assessing its seriousness and potential mitigation.

2) A comparison of the nature of SoC, and the effect of any variation on outcomes, to which the company responded:³ “*Across pegcetacoplan and iptacoplan trials, background standard of care is broadly similar, with both APPEAR-C3G and VALIANT showing predominant use of RAAS inhibitors and corticosteroids.*”

They went on to state that there are differences between VALIANT and APPEAR-C3G, but that: “...*the broadly similar use of RAAS inhibitors and corticosteroids suggests that these variations are unlikely to materially affect the incremental treatment effects observed. As such, while methodological and population differences should be acknowledged, they are not expected to introduce significant bias into the ITC results.*” However, they did draw attention to the effect of concomitant immunosuppressive therapy on decreasing the effectiveness of iptacoplan, based on a European Medicines Agency (EMA) report, and which does not apply to pegcetacoplan. The EMA report does support this claim, albeit without any supporting data: “*Patients with C3G treated with immunosuppressant medicinal products may show modest proteinuria reduction with iptacoplan, which is likely linked to a more treatment-resistant nature of C3G in these patients.*” (p.4) The EAG can also confirm that the subgroup analyses of VALIANT showed that the statistically significant effect on both proteinuria and eGFR change was maintained regardless of immunosuppressive status.⁹ This would suggest that there could be a bias in

the ITC in favour of iptacopan given the greater use of immunosuppressants in VALIANT versus APPEAR-C3G (37% vs 69%).³ It is also the case that the differences between VALIANT and APPEAR-C3G in other types of SoC seemed small: renin-angiotensin system (RAS) inhibitors (91% vs 97-100%; systemic corticosteroids (32-39 vs 29-36%); SGLT2 inhibitors (9-10% vs 5-6%). In conclusion, the differences in SoC between the two trials, although the treatment effect might favour iptacopan, does imply a key issue.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Results of proteinuria

The results of Bucher's indirect comparison of the primary outcomes from VALIANT and APPEAR C3G showed that after 6 months of treatment, pegcetacoplan was associated with a significantly greater reduction in uPCR from baseline compared with iptacopan (% mean difference (MD) = -50.90 [95% CI - 67.34 to -26.18]).¹

The results of analyses using the same uPCR measurement method by including only non-missing values of uPCR (24 hour) from VALIANT and non-missing only values of uPCR (FMU) from APPEAR C3G were consistent with results from the primary outcomes. The results also demonstrated that pegcetacoplan was associated with a statistically significant greater reduction in uPCR from baseline than iptacopan.¹

Pegcetacoplan resulted in a significantly higher probability of achieving a uPCR <1 g/g (risk difference (RD) = 0.26 [95% CI 0.06 to 0.46]), as well as achieving ≥50% reduction of UPCR (RD = 0.29 [[95% CI 0.01 to 0.58]) compared with iptacopan.¹ The comparisons on the basis of odds ratios (OR) did not reach statistical significance (uPCR <1 g/g: OR = 2.11 [95% CI 0.30 to 14.61]; uPCR ≥50% reduction: OR = 4.46 [95% CI 0.57 to 34.84]).¹

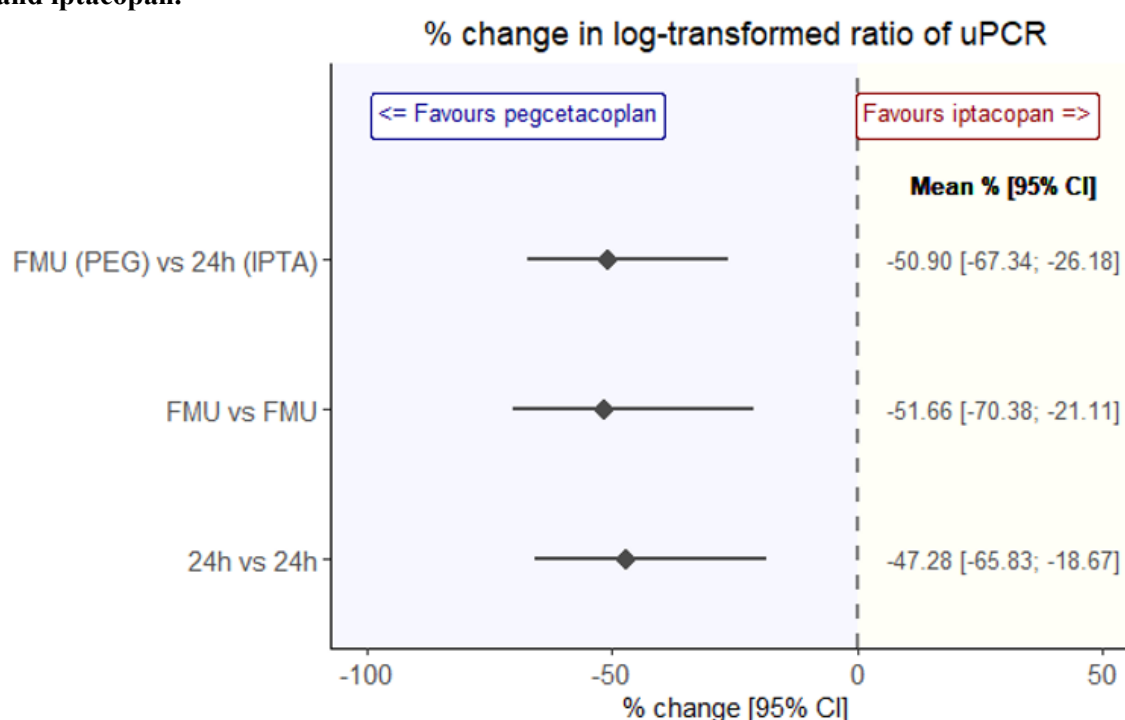
Table 3.52 below showed the results of Bucher's indirect comparison between pegcetacoplan and iptacopan for proteinuria-related outcomes. Figure 3.11 below shows the comparison of log (uPCR) percent change from baseline between pegcetacoplan and iptacopan.

Table 3.52: Results of Bucher's indirect comparison between pegcetacoplan and iptacopan for proteinuria-related outcomes.

Outcome	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
log(uPCR/uPCR baseline), mean % [95% CI]			
uPCR FMU vs FMU	-68.1 [-76.2; -57.3]	-34.1 [-55.5; -2.4]	-51.66 [-70.38; -21.11]
uPCR FMU vs 24h		-35.1 [-51.1; -13.8]	-50.90 [-67.34; -26.18]
uPCR 24h vs 24h	-65.8 [-75.4; -52.5]	-35.1 [-51.1; -13.8]	-47.28 [-65.83; -18.67]
uPCR thresholds (FMU vs 24h), risk difference [95% CI]			
≥3 (g/g)	-0.09 [-0.22; 0.05]	-0.10 [-0.32; 0.12]	0.01 [-0.24; 0.27]
1-3 (g/g)	-0.21 [-0.38; -0.04]	0.02 [-0.20; 0.25]	-0.23 [-0.51; 0.05]
<1 (g/g)	0.31 [0.15; 0.47]	0.05 [-0.07; 0.17]	0.26 [0.06; 0.46]
≥50% reduction	0.53 [0.29; 0.76]	0.23 [0.07; 0.40]	0.29 [0.01; 0.58]
uPCR thresholds (FMU vs 24h), odds ratio [95% CI]			

Outcome	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
≥3 (g/g)	0.56 [0.22; 1.41]	0.65 [0.25; 1.67]	0.87 [0.23; 3.26]
1-3 (g/g)	0.42 [0.20; 0.87]	1.11 [0.44; 2.76]	0.38 [0.12; 1.22]
<1 (g/g)	4.22 [1.89; 9.40]	2.00 [0.34; 11.66]	2.11 [0.30; 14.61]
≥50% reduction	30.90 [8.39; 113.77]	6.93 [1.41; 33.93]	4.46 [0.57; 34.84]
Based on Table 45 of CS ¹ 24h = 24-hour urine collection; All = all VALIANT patients; C3G = complement 3 glomerulopathy; CI = confidence interval; CS = company submission; FMU = first morning urine; IPTA = iptacopan, PEG = pegcetacoplan, uPCR – urinary protein to creatinine ratio			

Figure 3.11: Comparison of log (uPCR) percent change from baseline between pegcetacoplan and iptacopan.



Based on Figure 15 of CS¹

24h = 24-hour urine collection; CI = confidence interval; CS = company submission; FMU = first morning urine, IPTA = iptacopan; PEG = pegcetacoplan; uPCR = urinary protein to creatinine ratio

3.4.2 Results of renal function

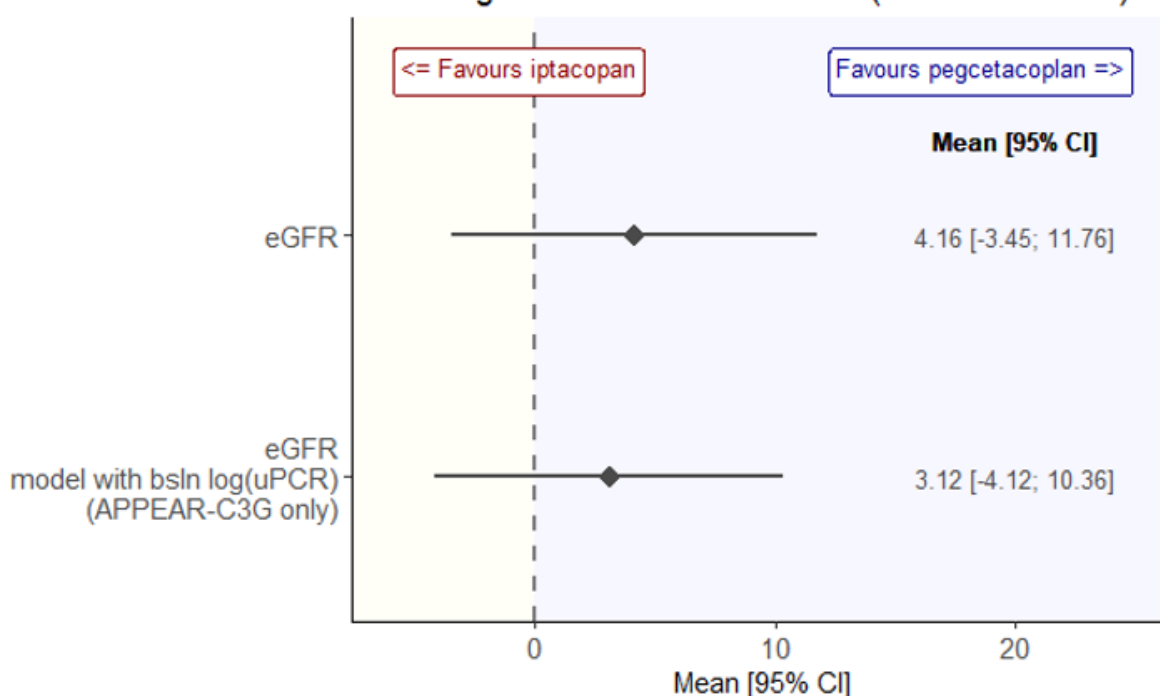
The results are shown in Table 3.53 and Figure 3.12.

Table 3.53: Results of Bucher's indirect comparison between pegcetacoplan and iptacopan for outcomes related to renal function.

Characteristics	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
Change from baseline, mean [95% CI]			

Characteristics	VALIANT (all patients)	APPEAR-C3G	VALIANT (All) VALIANT (All) vs APPEAR-C3G
	PEG vs Placebo	IPTA vs Placebo	PEG vs IPTA
eGFR (mL/min/1.73 m ²)	6.31 [0.50; 12.12]	2.156 [-2.75, 7.06] 3.19* [-1.13; 7.51]	4.16 [-3.45; 11.76] 3.12 [-4.12; 10.36]
Risk difference [95% CI]			
Composite renal endpoint	0.46 [0.21; 0.70]	0.23 [0.07; 0.40]	0.22 [-0.07; 0.52]
Stable eGFR (≤15% reduction)	0.09 [-0.08; 0.26]	0.01 [-0.14; 0.15]	0.09 [-0.13; 0.31]
Odds ratio [95% CI]			
Composite renal endpoint	27.48 [6.10; 123.85]	7.15 [1.43; 35.72]	3.85 [0.42; 34.84]
Stable eGFR (≤15% reduction)	1.49 [0.72; 3.12]	1.06 [0.24; 4.61]	1.41 [0.27; 7.26]
Source: Table 46, CS ¹ * model including baseline eGFR and log(UPCR) as covariates in APPEAR-C3G. All = all VALIANT patients; C3G = complement 3 glomerulopathy; CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; IPTA = iptacopan; PEG = pegcetacoplan			

Figure 3.12: Comparison of eGFR change from baseline between pegcetacoplan and iptacopan
Change from baseline in eGFR (mL/min/1.73 m²)



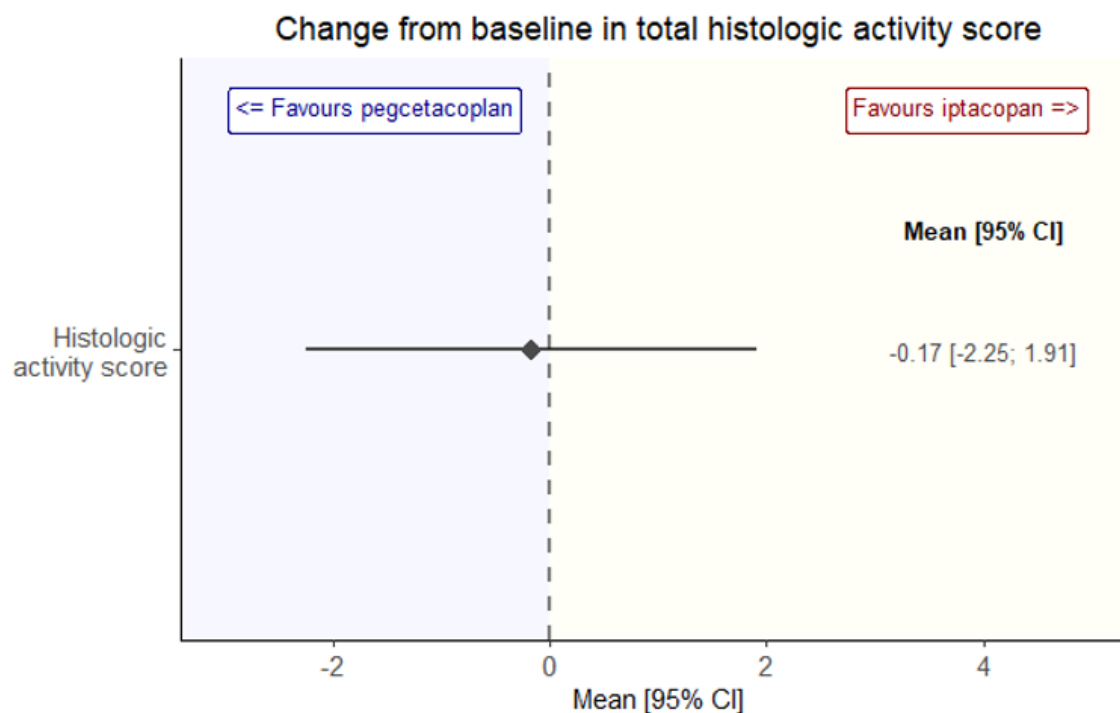
Source: Figure 15, CS¹

C3G = complement 3 glomerulopathy; CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; uPCR = urinary protein to creatinine ratio

3.4.3 Results of histological outcome and change in FACIT-Fatigue score

The results are shown in Figures 3.13 and 3.14

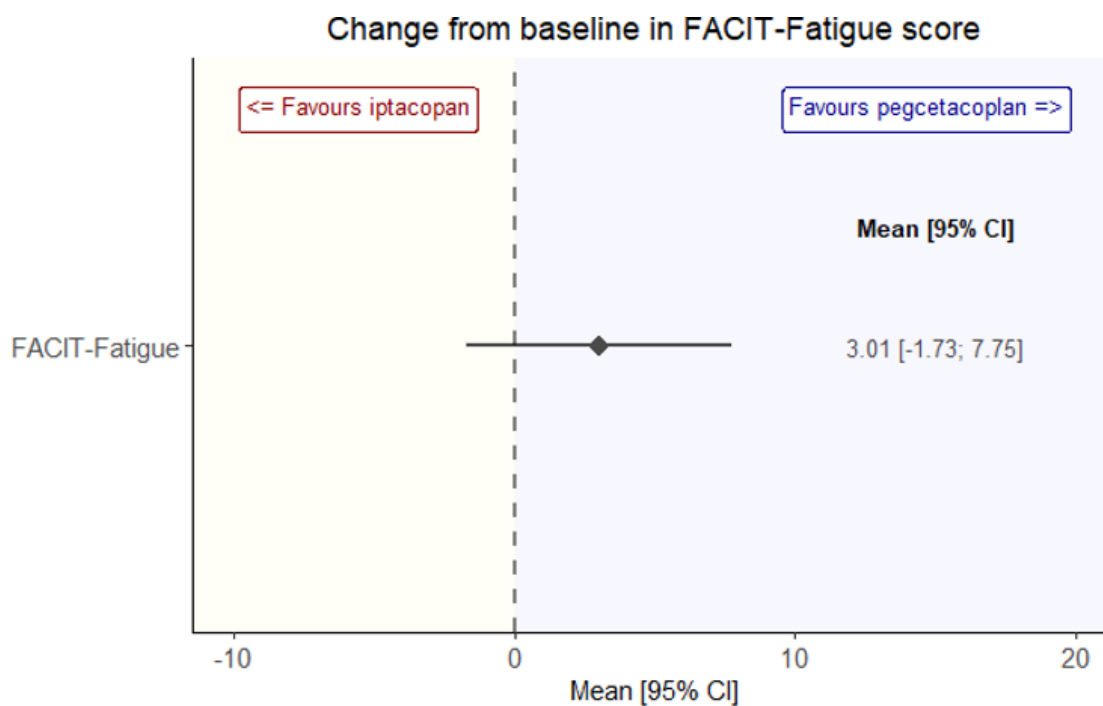
Figure 3.13: Comparison of C3G histologic index activity total score change from baseline between pegcetacoplan and iptacoplan



Source: Figure 17, CS¹

C3G = complement 3 glomerulopathy; CI = confidence interval; CS = company submission

Figure 3.14: Comparison of C3G histologic index activity total score change from baseline between pegcetacoplan and iptacoplan



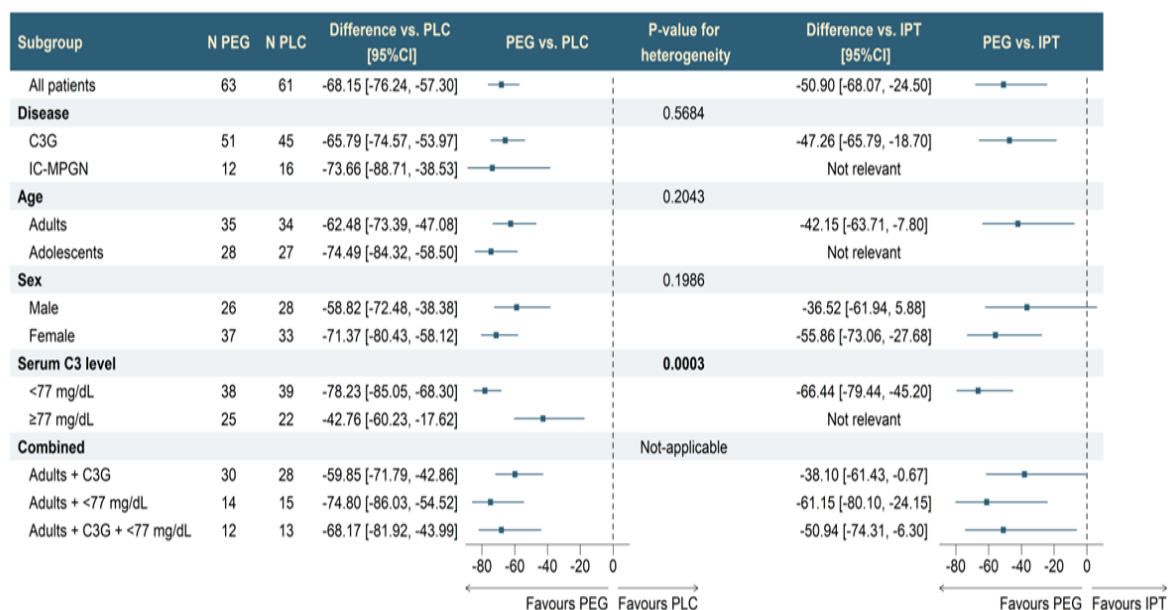
Source: Figure 18, CS¹

C3G = complement 3 glomerulopathy; CI = confidence interval; CS = company submission; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy - Fatigue

3.4.4 Subgroup analyses

Because of differences in eligibility criteria between VALIANT and APPEAR-C3G, subgroup analyses were conducted for three sets of outcomes by selecting data for VALIANT only from each of the subgroups and then combining with all data from APPEAR-C3G. The results are shown in Figures 3.15, 3.16 and 3.17.

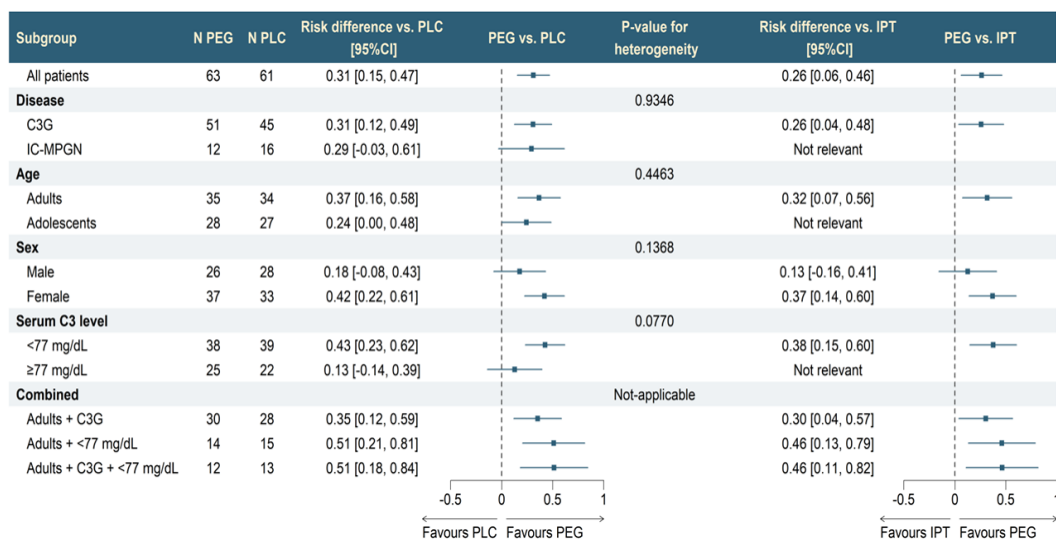
Figure 3.15: Subgroup analysis for indirect comparison between pegcetacoplan and iptacoplan for uPCR change from baseline.



Source: Figure 35, Appendix C⁹

C3G = complement 3 glomerulopathy; CI = confidence interval; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; IPT = iptacoplan; PEG = pegcetacoplan; PLC = placebo; uPCR = urinary protein to creatinine ratio

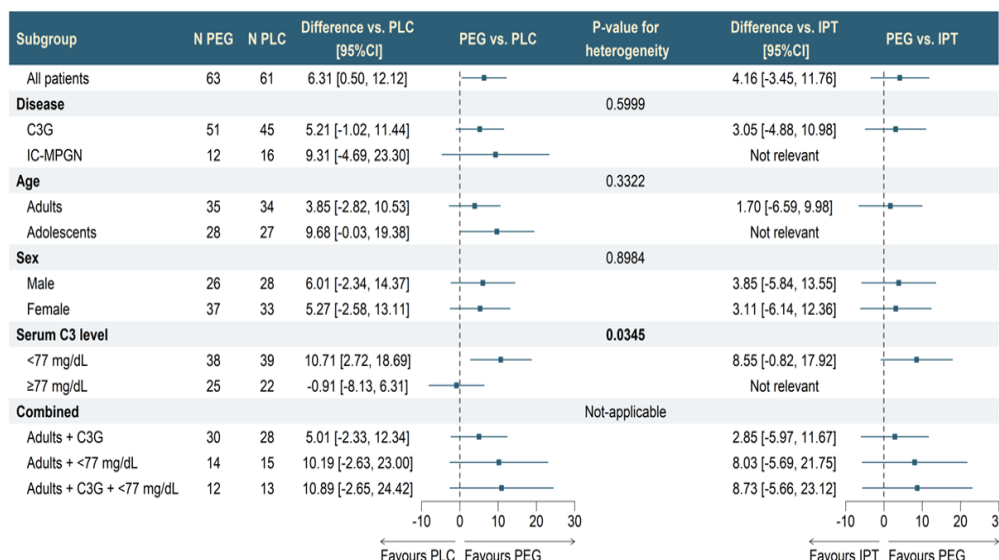
Figure 3.16: Subgroup analysis for indirect comparison between pegcetacoplan and iptacoplan regarding the reduction in uPCR <1 g/g



Source: Figure 37, Appendix C⁹

C3G = complement 3 glomerulopathy; CI = confidence interval; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; IPT = iptacopan; PEG = pegcetacoplan; PLC = placebo; uPCR = urinary protein to creatinine ratio

Figure 3.17: Subgroup analysis for indirect comparison between pegcetacoplan and iptacopan regarding eGFR change from baseline



Source: Figure 39, Appendix C⁹

C3G = complement 3 glomerulopathy; CI = confidence interval; eGFR = estimated glomerular filtration rate; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; IPT = iptacopan; PEG = pegcetacoplan; PLC = placebo

EAG comment: The results of the ITC show an advantage to pegcetacoplan over iptacopan in all three outcome sets according to the point estimates. Also, the 95% CI for the outcome that was the primary one in the VALIANT trial does not cross the point of no difference. However, the difference between pegcetacoplan and iptacopan was not significant for the other outcomes.

The subgroup analyses revealed that there was little effect of differences between the trials in population characteristics i.e., disease type (C3G or IC-MPGN), age (adults or adolescents), sex or serum C3 level (< or ≥77 mg/dL). One exception seemed to be an increase in the eGFR advantage to pegcetacoplan with the subgroup of serum C3 level that better matched the APPEAR-C3G trial where the 95% CI only slightly overlapped the point of no difference.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS, Appendix B and response to clarification^{1,3,6} provided sufficient details for the EAG to appraise the searches conducted to identify relevant clinical evidence on efficacy and safety outcomes of treatments for C3G and primary IC-MPGN. Searches were conducted in September 2024 and updated in May 2025. Additional searches were conducted on 9 October 2025 in response to a request for clarification by the EAG. Searches were transparent and reproducible, and comprehensive strategies

were used. A good range of bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The study selection criteria for participants, interventions, comparators and outcomes in the SLR of clinical effectiveness generally encompassed those specified by the NICE final scope. The company have not adequately described their methods for performing quality assessment. The number of studies retrieved, screened and included was clear based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart.

One pivotal phase 3 RCT was identified as being relevant to the SLR: one phase 3 RCT (VALIANT) provided the main source of evidence. The VALIANT study is a pivotal phase 3, randomised, placebo-controlled, double-blinded, multicentre study to evaluate the efficacy and safety of twice-weekly SC infusions of pegcetacoplan in patients diagnosed with C3G or primary IC-MPGN. The open-label phase 2 RCT (NOBLE) and an open label extension study were identified that provided supportive evidence of the clinical efficacy of pegcetacoplan for the treatment of patients with C3G or primary IC-MPGN. The NOBLE trial was a multinational, prospective phase 2 RCT that assessed the efficacy and safety of 12 weeks of pegcetacoplan or standard of care in adult patients with recurrent C3G or IC-MPGN after kidney transplant. The open label extension study (VALE) provided data on the long-term clinical efficacy and safety of pegcetacoplan for the treatment of patients with C3G or primary IC-MPGN.

The results of the VALIANT trial showed that improvement in the primary outcome, log-transformed FMU uPCR, appears to be maintained at the 26-week RCP, and up to at least 52 weeks. However, it appears that there was a gradual decrease in the improvement in outcomes for those randomised to pegcetacoplan after the end of the randomised controlled period of 26 weeks in VALIANT. This includes eGFR, which showed that the change from baseline was -1.49 (95% CI -5.89 to 2.89) at 26 weeks, and -3.65 (95% CI -8.93 to 1.62) at 52 weeks. Therefore, the treatment effect (i.e., difference in outcomes between pegcetacoplan and placebo) might also diminish if patients in the placebo arm had continued on placebo instead of switching to pegcetacoplan. This means that there was potential long-term treatment effect waning for the pegcetacoplan plus standard of care versus standard of care, which implies a key issue.

Furthermore, on the basis of the subgroup analyses of the VALIANT trial, the results of subgroup analysis in terms of disease, age or transplant status were generally consistent with the results of the primary analyses. However, it should be noted that, on the basis of the results of subgroup analyses in terms of baseline C3 level, there were significant differences in the outcomes of proteinuria and eGFR at week 26 between the subgroup of baseline low C3 level and the subgroup of baseline normal C3 level. This means that baseline C3 level is a potential treatment effect modifier. Given that baseline C3 level is a potential treatment effect modifier, the company did not conduct relevant scenario analyses for the assessment of cost effectiveness. Therefore, there was uncertainty on the impact of this potential treatment effect modifier on the cost effectiveness assessment, which implies a key issue.

There were generally similar proportions of patients who experienced serious treatment-related adverse events between the pegcetacoplan treatment arm (9.5%) and the placebo arm (9.8%) during the randomised period (26 weeks) of the VALIANT trial. Only 1.9% of patients who experienced serious treatment-related adverse events were reported during the trial period of VALE.

In terms of the ITC analysis, the company conducted Bucher's indirect comparison to estimate the relative treatment efficacy between pegcetacoplan and iptacoplan. The ITC results of the primary outcomes from VALIANT and APPEAR C3G showed that after 6 months of treatment, pegcetacoplan was associated with a significantly greater reduction in uPCR from baseline compared with iptacoplan

(% MD = -50.90 [95% CI - 67.34 to -26.18]). The EAG considered the Bucher's ITC analysis used by the company to be an appropriate approach. However, there were concerns relating to the heterogeneity of populations in the ITC trials. It should also be noted that there were differences between ITC trials in standard of care. These limitations may have introduced uncertainty on the validity of the results of ITC. However, it should be noted that during the late stage of the appraisal of pegcetacoplan, the recent NICE guidance (published on 29 October 2025) stated that NICE was unable to make a recommendation on iptacopan for treating complement 3 glomerulopathy in adults, because the company has withdrawn from the appraisal.⁴ Therefore, iptacopan is no longer included as a comparator for this appraisal of pegcetacoplan. Given that it happened during the late stage of the appraisal of pegcetacoplan, we have included the ITC sections in the report for this appraisal of pegcetacoplan, although key issues 5 and 6 might be considered as of little importance or resolved.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 *Searches performed for cost effectiveness Section*

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, health-related quality of life (HRQoL) and cost/healthcare resource use identification presented in the CS.¹ The CADTH evidence-based checklist for the PRESS, was used to inform this critique.⁵ The EAG has presented only the major limitations of each search strategy in the report.

Appendices E, F and G of the CS provide details of searches conducted to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use in patients with C3G or primary IC-MPGN.¹⁰⁻¹² The searches were conducted in September 2024 and updated in May 2025.

EAG comment:

- A single set of searches was undertaken to identify relevant studies on cost effectiveness, health related quality of life and cost/health care resource use in the treatment of C3G and primary IC-MPGN. The CS, Appendices E, F and G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 3, 10-12}
- The following databases were searched on 2 September 2024, and updated on 27 May 2025: Embase, MEDLINE (including the Epub Ahead of Print, In-Process, In-Data Review & Other Non-indexed Citations, Daily and Versions segments of MEDLINE), CDSR, CENTRAL, Database of Abstracts of Reviews of Effects (DARE), Cochrane Methodology Register, NHS Economic Evaluations Database (NHS EED), Health Technology Assessment (HTA) Database, and the American College of Physicians (ACP) Journal Club.
- Journal publications were restricted to a publication date limit of 2014 - 2024, and congress abstracts were restricted to 2022 - 2024. No language limit was applied to any of the searches.
- The conferences of six key organisations were reviewed for relevant abstracts between 2022-2024 where available: American Society of Nephrology (ASN), European Renal Association (ERA), International Society for Pharmacoeconomics and Outcomes Research (ISPOR; US and European congresses), UK Kidney Week, World Congress of Nephrology (WCN) and the Southwest Nephrology Congress.
- The websites of the following HTA organisations were searched: NICE, Scottish Medicines Consortium (SMC), Canada's Drug Agency (CDA) and Pharmaceutical Benefits Advisory Committee (PBAC), and the following grey literature sources were searched: Cost-Effectiveness Analysis (CEA) Registry, EuroQoL website, Research Papers in Economics (RePEc), MAPI Institute, National Institute for Health Research HTA, International Network of Agencies for HTA, University of Sheffield Centre for Health and Related Research (SCHARR) health utility database, and the Institute for Clinical and Economic Review (ICER).

- All database strategies searched for a range of terms for C3G and primary IC-MPGN. This was then combined with study design filters containing terms for costs and economic evaluations, cost/healthcare resource use and HRQoL.
- The EAG noted that EMTREE indexing terms were used in the MEDLINE search strategy, rather than the MeSH equivalent. Although mapping between indexing terms does take place, it is good practice to use the database-appropriate subject headings to ensure no potentially relevant records are missed.
- The update searches were conducted by applying a 2024 publication year limit to the original searches. The EAG believed that the use of additional database fields (such as record entry date or update date) would have increased the chance of retrieving records with a pre-2024 publication date which had been added to the database since the date of the original search. Given the small number of records, a simpler approach would have been to re-run the searches in their entirety and deduplicate the results against those already found.
- All searches were well structured, transparent and reproducible and searches contained a good range of search terms, synonyms and subject headings. None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.1.

Table 4.1: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Patients with primary C3G (including DDD and C3GN) and primary or idiopathic IC-MPGN	Patients with secondary C3G/IC-MPGN
Intervention	Any treatments	None
Comparator	Any treatments	None
Outcomes(s) 1 (Published economic evaluations)	Model specifications, data inputs and assumptions Cost effectiveness results, such as: health costs, health benefits (overall survival), progression-free survival, other benefits modelled, life years and QALYs If relevant, submission outcome, reported limitations and criticisms	Outcomes not relating to economic evaluations, resource use, costs, and QoL/utilities
Outcomes(s) 2 (Utility studies)	Studies reporting utilities and disutility's for the population of interest using any utility measure, including (but not limited to) the following: EQ-5D (3L or 5L), HUI, SF-6D,	Outcomes not relating to economic evaluations, resource use, costs, and QoL/utilities

	Inclusion criteria	Exclusion criteria
	SF-36, standard gamble and time trade-off.	
Outcomes(s) 3 (Cost/resource use studies)	Direct medical costs, such as: healthcare and social care provision covering the cost of hospitalisation, outpatient follow-up, residential and day care, pharmaceutical interventions, laboratory testing Indirect costs (including loss of productivity [e.g., WPAI] and caregiver costs) Social impact (direct and indirect non-medical costs)	Outcomes not relating to economic evaluations, resource use, costs, and QoL/utilities
Study design 1, 2, 3	Any study type, including economic models and evaluations	Animal/in vitro studies Case reports, case series Systematic and narrative reviews Review, editorial, letter, protocol-only publications
Based on Appendix E (Table 117), Appendix F (Table 122), Appendix G (Table 124) C3G = complement 3 glomerulopathy; C3GN = C3 glomerulonephritis; DDD = dense deposit disease; EQ-5D = European Quality of Life-5 Dimensions; HUI = Health Utilities Index; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; QALY = quality-adjusted life year; QoL = quality of life; SF-36 = 36-item Short-form Health Survey; SF-6D = Short-form 6 Dimensions; WPAI = Work Productivity and Activity Impairment		

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

4.1.3 Conclusions of the cost effectiveness review

Although several technology appraisals (TAs) were listed in CS Section 3.4.4, no more details were provided there nor in the corresponding CS Appendix F.¹¹ The EAG noticed that the company's SLRs and review of prior NICE TAs seem less comprehensive in comparison to GID-TA11331,¹³ a recent NICE TA on C3G, and the company did not extend them (to the broader CKD population) for the most part although requested by the EAG at several instances during the clarification phase. The report draft on the SLR of health state utility values (HSUV) provided upon clarification proved mostly unreadable due to a formatting issue.¹⁴

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with reference case
Perspective on costs	NHS and PSS	The company modelled cost savings and QALY gains by accounting for reallocation of kidneys no longer required for patients treated with pegcetacoplan or iptacopan to the wider NHS population (i.e. other patients on the NHS transplant waiting list).
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Consistent with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Partly inconsistent with reference case: Sidhu et al., informing the CKD 3-5 health states, used the US tariff.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with reference case

Element of health technology assessment	Reference case	EAG comment on CS
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with reference case
CS = company submission; CKD = chronic kidney disease; EQ-5D = European Quality of Life-5 Dimensions; NHS = National Health Service; PSS = personal social services; QALY = quality-adjusted life year; US = United States		

4.2.2 Model structure

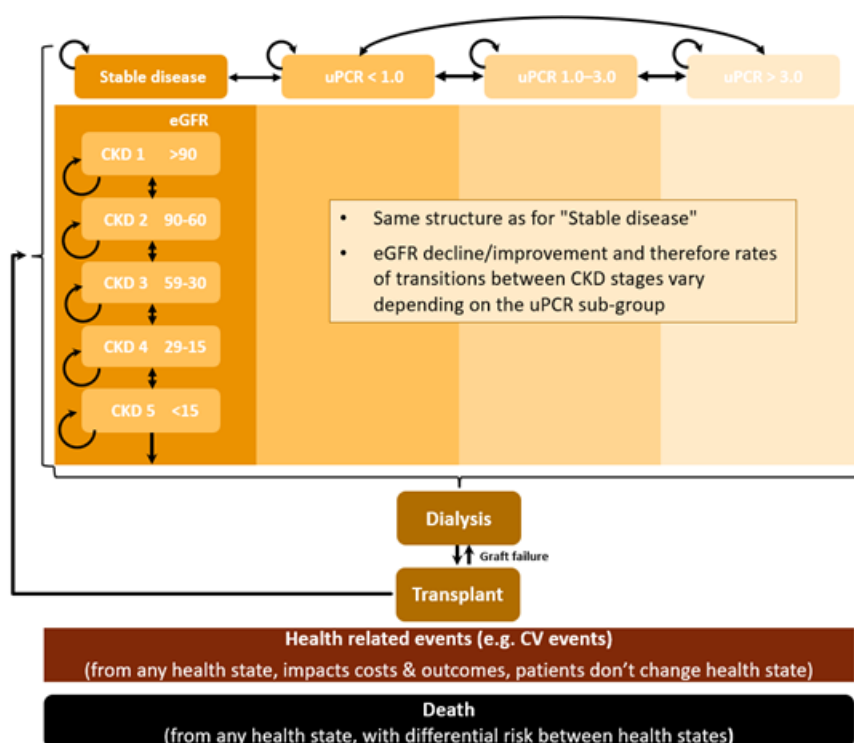
A de novo cost effectiveness model was developed using a cohort-level state-transition (Markov) approach to simulate the progression of CKD through to end-stage kidney disease (ESKD), including peritoneal dialysis (PD), haemodialysis (HD), and kidney transplantation. The economic model comprises health states based on three uPCR categories and one stable disease category, which were stratified across five CKD stage. Six additional health states included HD, PD, HD unsuitable for transplant, PD unsuitable for transplant, transplant and death. Health states were replicated for post-transplant patients, totalling the number of health states to 49 (Figure 4.1):

- Pre-transplant (25 health states): 4x uPCR (including stable disease) categories with 5x CKD categories in each, 4x dialysis [PD, HD, PD unsuitable for transplant, HD unsuitable for transplant], and 1x transplant
- Post-transplant (23 health states): 4x uPCR (including stable disease) categories with 5x CKD categories in each, 2x dialysis [PD & HD], and 1x transplant
- Death (1 health state).

Key model assumptions (iptacopan + SoC is currently not considered a relevant comparator and the information on iptacopan + SoC below might be obsolete, but was included for completeness):

- Disease progression assumptions
 - eGFR decline and transitions between CKD stages vary depending on uPCR level, with higher uPCR levels associated with more rapid eGFR decline.
 - For patients achieving stable disease, uPCR and eGFR levels are assumed to remain unchanged and patients discontinue all treatment. Treatment is assumed to be resumed upon disease relapse. Median time to relapse of 26 months from Caravaca-Fontán (2020) was assumed, which was converted into a per-cycle relapse probability of 7.69%.
 - Technically, all transitions between any combination of CKD and uPCR health states are allowed.
 - Patient with large variation from normal eGFR levels (i.e., ~90 mL/min per 1.73 m²) have an increased risk of cardiovascular (CV) events such as heart failure, stroke, coronary heart disease, and cardiovascular mortality.
 - Death was modelled as an absorbing state and could be reached from any other health state. The risk of mortality was assumed dependent on CKD state (i.e., risk increases with CKD state).
- Treatment-related assumptions
 - uPCR and CKD stage transitions were based on a multinomial and linear regression model respectively, including the open-label period (i.e., 52 weeks of follow-up data) for pegcetacoplan + SoC while 26 weeks of placebo follow-up data were used for SoC from VALIANT.

- The uPCR transitions for iptacopan + SoC were informed by an ITC of pegcetacoplan + SoC and iptacopan + SoC. The rate of eGFR decline for iptacopan + SoC was assumed to be the same as for pegcetacoplan + SoC, conditional on the corresponding uPCR level.
- Patients discontinuing pegcetacoplan + SoC were assumed to receive SoC alone after which no residual pegcetacoplan treatment effect was assumed.
- Patients who progress to CKD stage 5 or require dialysis were assumed to discontinue treatment regardless of treatment.
- For post-transplant patients who do not achieve stable disease, treatment is continued if they did not discontinue treatment before transplant. The same treatment (relative) effectiveness as pre-transplant is assumed.
- Assumptions related to initiation of dialysis and transplantation
 - After remaining in CKD stage 5 for one cycle, regardless of treatment, 87% of patients transition to dialysis and 13% of patients have a transplant.
 - All patients were assumed to commence dialysis and/or kidney transplantation when reaching ESKD; conservative management was not considered.
- Dialysis and transplantation assumptions
 - While in the dialysis or CKD5 health states, patients had a (time independent) probability of receiving a transplant each cycle.
 - A probability of graft survival was applied to patients in the transplant state in the first cycle following transplantation. Patient experiencing graft failure transition back to the dialysis health states, in which the same (time independent) per cycle probability of receiving a (next) transplant applies.
 - Following a transplant, patients are assumed to have a uPCR level <1.0 g/g. In subsequent cycles, the expected rate of increase in proteinuria as observed in the VALIANT placebo arm is applied.
 - The model allowed for multiple transplant-graft failure cycles over the model time horizon.
 - The model accounts for different dialysis modalities in estimating costs and utilities: HD and PD.
 - Modality proportions: 88% of patients was assumed to undergo HD and 12% PD, based on data provided by United Kingdom Renal Registry (UKRR) 27th annual report.
 - Cost valuation: annual dialysis costs were derived from the NHS Schedule of Reference costs. HD was assumed to occur three times per week, and PD once daily.
 - Utility valuation: utility values of 0.44 and 0.53 were used to inform HRQoL in the HD and PD health states respectively.
 - Additional cost savings and quality-adjusted life year (QALY) gains beyond the CS population were modelled for patients on pegcetacoplan + SoC or iptacopan + SoC, resulting from reallocation of kidneys no longer required to other patients on the NHS transplant waiting list.

Figure 4.1: Model structure

Based on Figure 1 of the company's clarification response

CS = company submission; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; uPCR = urinary protein to creatinine ratio

EAG comment: The main concerns of the EAG relate to: a) inclusion of a stable disease health state, b) the complexity of the model structure, c) modelling of the initiation of dialysis and transplantation, and d) the assumption that patients return to the baseline uPCR levels distribution following transplantation.

- a) The company's model includes a stable disease health state, defined by uPCR <0.5 g/g. However, as discussed in more detail in Section 4.2.6, this health state lacks empirical justification and appears structurally redundant. Its inclusion introduces structural complexity without clear clinical rationale and has a notable impact on cost effectiveness outcomes. Hence, the EAG has excluded this health state from its base-case analysis.
- b) The EAG noted the complexity of the company's economic model, comprising 49 distinct health states, primarily informed by the VALIANT study with 63 and 61 patients in the pegcetacoplan and placebo study arms respectively (CS Table 12). The initial inclusion of tunnel states further contributed to this complexity but were removed in response to the clarification letter. Removal did not alter the cost effectiveness outcomes, suggesting limited structural necessity. A key structural feature of the company's initial schematic model structure (CS Figure 19) was the possibility of bidirectional transitions between uPCR subgroups and CKD stages. This raised concerns to the EAG in terms of clinical plausibility, specifically transitions to earlier CKD stages due to increasing eGFR rates which may not reflect typical disease progression in C3G/IC-MPGN. Nonetheless, the EAG clinical expert acknowledged that "*in some scenarios, eGFR may even rise, therefore going to a milder CKD stage*" supporting the inclusion of such transitions under certain conditions. In response to clarification question B4, the company explained that long-term improvements in eGFR for this population

were unlikely based on clinical feedback received, and such transitions were therefore not included in their base-case analysis. Upon request by the EAG, the company also provided a comparison of their current model structure with the model structure in GID-TA11331 (i.e., iptacopan for treating C3G). This appraisal employed a simpler model structure, omitting uPCR health states and consolidating post-transplant outcomes into a single health state. Compared to other appraisals in the field of CKD, a model structure similar to GID-TA11331 was used in TA937 (i.e., targeted-release budesonide for treating primary immunoglobulin A (IgA) nephropathy), whereas the TA1074 (i.e., sparsentan for treating primary IgA nephropathy) model structure closely aligned with the current model structure, albeit with different uPCR thresholds (<0.44g/g, 0.44–0.88g/g, 0.88–1.76g/g, >1.76g/g). The EAG expert stated on this that “*capturing urine P:Cr down to 0.5g/g or 1g/g would have been preferable where progression is far less likely*”. Overall, acknowledging the trade-off between complexity and reflectiveness of clinical reality in the process of model conceptualisation, the EAG considers the company’s model structure complex but reasonable. However, also considering the relatively low patient numbers in VALIANT, exploring a more simplistic model structure (e.g., including a single post-transplant health state) would be informative.

- c) The EAG questions the company’s assumption that all patients initiate dialysis or undergo transplantation one model cycle after entering the CKD stage 5 health state, effectively limiting time in CKD 5 to three months. This assumption is not in line with NICE guideline NG107, which recommends initiating kidney replacement therapy (KRT) at an eGFR of approximately 5–7 mL/min/1.73 m². Also in GID-TA11331 (iptacopan for treating C3G), a lower threshold of 7.6 mL/min/1.73 m² was assumed. In response to clarification, the company stated that it does not apply an explicit eGFR threshold but rather uses a time-dependent transition validated through clinical interviews. Experts indicated that for patients with glomerular diseases such as C3G/IC-MPGN, KRT may be considered at higher eGFR levels (10–15 mL/min/1.73 m²) due to more aggressive disease progression and symptom burden. The EAG clinical expert, however, noted that “*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. The EAG requested scenario analyses in which alternative eGFR thresholds to initiate dialysis and transplantation were explored, but the company stated that this was not feasible due to the explicit link between time to dialysis and the model’s cycle length. Alternatively, it provided scenarios reducing the proportion of patients transitioning from CKD 5 to dialysis, which had minimal impact on cost effectiveness results. However, the EAG considers these scenarios suboptimal, and would like to see scenarios using eGFR thresholds consistent with NG107 and GID-TA11331. As patients receiving iptacopan + SoC or SoC alone progress more rapidly than those treated with pegcetacoplan + SoC, such scenarios are expected to increase the incremental cost-effectiveness ratio (ICER).
- d) The EAG considers the company’s assumption that patients return to the baseline distribution of uPCR levels sourced from VALIANT following transplantation to be insufficiently justified and clinically implausible. This assumption failed to account for the expected uPCR reduction post-transplant, which typically reflects improved renal function and minimal leakage from residual native kidneys. In response to the clarification letter, the company acknowledged the limitations of the original approach and revised its base-case assumptions. Based on clinical expert feedback, the company in their revised base-case assumes that all patients enter the transplant health state with uPCR <1.0 g/g, reflecting minimal proteinuria immediately post-

transplant. In the subsequent cycle, ■ of patients remain in the <1.0 g/g subgroup, while ■ transition to the 1.0–3.0 g/g subgroup, based on the uPCR rate increase observed in the placebo arm of the VALIANT trial. The EAG clinical expert also noted that “*immediately following transplant, urine P:Cr likely falls to a minimum, before onset of proteinuria due to disease recurrence*”. Although the EAG considers the company’s updated post-transplant modelling approach more clinically plausible than its original approach, it would like to see a more simplistic scenario analysis including a single post-transplant health state in line with GID-TA11331.

4.2.3 Population

Consistent with the proposed Medicines and Healthcare Products Regulatory Agency (MHRA) label population, the NICE scope, as well as the pivotal randomised trial (VALIANT), the population considered in the CS (CS Table 1) was adolescents (aged 12-17 years) weighing at least 42 kg and adult patients with primary C3G or IC-MPGN. The key baseline patient characteristics in the economic model are listed in Table 4.3 below.

Table 4.3: Baseline patient characteristics used in the economic model

		Value	Use in the economic model
Age (mean)		25.97 years	Mortality risk, general population age/sex disutility
Weight (mean)		63.09 kg	SoC basket costs
Percentage male		43.55%	Mortality risk, general population age/sex disutility
Baseline distribution of CKD stages	CKD 1	45.97%	Starting health state distribution
	CKD 2	20.97%	
	CKD 3	29.84%	
	CKD 4	3.23%	
	CKD 5	0.00%	
Baseline distribution of uPCR levels	<1g/g	8.87%	
	1-3 g/g	58.87%	
	>3g/g	32.26%	
Based on CS Table 61 ¹			
CKD = chronic kidney disease; CS = company submission; SoC = standard of care; uPCR = urinary protein to creatinine ratio			

EAG comment: The main concerns of the EAG relate to: a) lack of subgroup analyses, and b) generalisability of the modelled patient baseline characteristics to UK clinical practice.

- a) In their initial submission, the company did not provide the subgroup analyses specified in the NICE scope. This decision was justified on the basis that subgroup analyses from the VALIANT trial showed consistent treatment effects across key subpopulations, with no statistically significant differences observed in proteinuria or eGFR outcomes. The company also cited the rarity of the conditions and limited subgroup sizes as a constraint. However, the EAG considers this justification insufficient. Even in the absence of statistically significant differences in treatment efficacy, subgroup-specific cost effectiveness outcomes may still vary due to differences in baseline risks, HRQoL, resource use, and associated costs. In response to clarification, the company provided

subgroup analyses for the following subgroups: IC-MPGN versus C3G, non-transplant versus post-transplant, and adolescents versus adults. The EAG noted that cost effectiveness outcomes differed substantially between the non-transplant and post-transplant subgroups, as well as between adolescents and adults. However, these results should be interpreted with caution due to the limited sample sizes in these subgroups (at baseline only 9 patients (both VALIANT arms) were post-transplant, CS Table 13).

- b) The EAG questions the generalisability of the modelled patient baseline characteristics, which were derived from the VALIANT trial population, to UK clinical practice. Notably, only 3% of patients in VALIANT were in CKD stage 4 at baseline, and no patients were in CKD stage 5. Furthermore, the trial population was predominantly composed of C3G patients (77%). In response to clarification, the company stated that clinical opinion indicated that the VALIANT baseline characteristics are broadly aligned with the expected UK treatment population for pegcetacoplan. UK clinicians confirmed that CKD stage 4 patients may be considered for treatment, particularly where active glomerular disease is present and irreversible damage is absent. Chronic kidney disease stage 5 patients are generally not treated as the kidneys are likely to be irreversibly damaged. The company also provided a comparison between VALIANT and APPEAR-C3G (iptacopan), noting that the VALIANT trial had a lower mean baseline eGFR, indicating that patients had slightly more advanced kidney impairment than those in APPEAR-C3G. The EAG clinical expert noted that baseline age, gender, and CKD stage distributions in VALIANT fairly reflect UK RaDaR data, and that weight distributions are consistent with UK age and gender matched norms. Median uPCR would be expected to be in the higher bracket (>3g/g), but after 6-12 months is expected to range between <1 g/g to >3 g/g. Despite the limited representation of advanced CKD stages and differences with the APPEAR C3G, the EAG considers the modelled baseline characteristics to be sufficiently generalisable to UK clinical practice. Further subgroup analyses on CKD stage could be informative to explore the potential impact of different CKD distributions on the cost-effectiveness results.

4.2.4 Interventions and comparators

The intervention considered in the CS was pegcetacoplan as an add-on to SoC, administered twice weekly (by a healthcare professional or by the patient or caregiver following proper instructions) as a 1,080 mg subcutaneous infusion with a commercially available syringe system infusion pump. This is consistent with the anticipated licensed indication.

The comparators considered in this appraisal were SoC (informed by Kidney Disease: Improving Global Outcomes guidelines), including ACEi/ARB (■%), immunosuppressants (■%), systemic corticosteroids (■%) and SGLT2 inhibitors (■%), and iptacopan as an add-on to SoC (iptacopan + SoC is currently not considered a relevant comparator and information on iptacopan + SoC might be obsolete, but was included for completeness). The company considered SoC to be comparable to the placebo arm in VALIANT, whereas the efficacy of pegcetacoplan + SoC was compared to iptacopan + SoC using an indirect treatment comparison.

Eculizumab was included in the NICE scope for people who have previously had a kidney transplant and who have highly aggressive C3 glomerulopathy recurrence as specified in the NHS England clinical commissioning policy for eculizumab. However, the company did not include eculizumab as a comparator due to limited evidence regarding its widespread use in clinical practice in the UK and the lack of robust data confirming its efficacy in stabilising eGFR and reducing uPCR in patients with C3G.

EAG comment: The main concerns of the EAG relate to: a) representativeness of the composition (based on Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines) and distribution (as observed in VALIANT) of SoC for UK clinical practice, and b) the exclusion of eculizumab as comparator.

- a) It is unclear to the EAG whether the composition and distribution of SoC in the company's economic model is representative of UK clinical practice. In response to clarification question B6, the company stated that according to their clinical experts, the KDIGO guidelines informing the composition of the SoC basket are in the process of being updated. Nevertheless, the clinical experts agreed that the treatments and proportions used in the modelled SoC basket are generalisable to UK practice, with the exception of SGLT2 inhibitors which they assumed will be used in more patients in the future. The EAG clinical expert agreed that UK clinicians generally follow KDIGO in C3G/IC-MPGN, with the caveat that SoC is an accepted practice based on experience rather than evidence.
- b) Contrary to the final NICE scope, eculizumab was not included as a comparator in the economic model for people who have previously had a kidney transplant and who have highly aggressive recurrent disease as specified in the NHS England clinical commissioning policy for eculizumab. In response to clarification question A7 and B7, the company stated that *“due to time constraints and committee agreement during the iptacopan appraisal that eculizumab is not an appropriate comparator, as well as the lack of eculizumab data, an economic comparison with pegcetacoplan was not conducted”*. Further details of the EAGs view on this are described in Section 2.3.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is three months with a lifetime time horizon and a half-cycle correction is applied. Additionally, the company modelled cost savings and QALY gains by accounting for reallocation of kidneys no longer required for patients treated with pegcetacoplan or iptacopan to the wider NHS population (i.e., other patients on the NHS transplant waiting list).

EAG comment: The company included cost savings and QALY gains associated with the reallocation of kidneys no longer required by patients treated with pegcetacoplan or iptacopan. Next to issues with the approach to estimate these costs, the EAG is concerned that these cost savings and health benefits fall outside the scope of the NICE reference case, which specifies a perspective limited to the NHS and PSS. In their response to the clarification letter, the company argues that their approach is consistent with NICE's reference case by stating that the NICE Health Technology Evaluation Manual (PMG36) does not limit the reference case to costs and benefits incurred only by patients with the condition under evaluation. In addition, it referred to TA809 (imlifidase for desensitisation before kidney transplantation), in which the committee concluded that kidneys are a scarce resource and that decisions should consider opportunity costs alongside equity of access. The EAG noted that the NICE reference case focuses on costs and outcomes relevant to the NHS and PSS, but primarily in relation to the population under appraisal. Although the manual allows for consideration of health effects on carers and other individuals, this is typically limited to those directly affected by the condition or its treatment (as seems to be the case in TA809, in which the intervention facilitates access to transplantation for the treated population). The EAG considers that the health benefits and cost savings accruing to patients outside the C3G/IC-MPGN population represent indirect effects which are not directly attributable to the intervention's impact on the treated population (or their carers) and therefore may not be appropriate for inclusion in the company's base-case. Consistent with the NICE manual for non-reference-case

analyses, any benefits and cost-savings from kidney reallocation should be presented in a disaggregated format, separately from the reference-case results. Hence, cost savings and QALY gains associated with the reallocation of kidneys no longer required by patients treated with pegcetacoplan were excluded from the EAG base-case.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Regression models

The company estimated treatment effectiveness and extrapolated outcomes using two separate regression models: one for uPCR and one for eGFR decline used to inform effectiveness for both pegcetacoplan + SoC and SoC only. Models were fitted to individual patient-level data from the VALIANT trial (R version 4.4.2), using baseline data (for both strategies), 26-week placebo data (assumed to represent SoC), and 52-week pegcetacoplan data, i.e., intermediate measurements were not included, and only for pegcetacoplan + SoC the open-label period was considered (CS Figure 5, CS Table 10).

4.2.6.1.1 uPCR state transitions

For uPCR state transitions, both ordered logistic and multinomial logistic regression models were explored. Candidate covariates included:

- Health state during previous visit (uPCR <1.0 g/g, uPCR 1.0 - 3.0 g/g, uPCR >3 g/g)
- Treatment (pegcetacoplan, no pegcetacoplan)
- Age
- Sex

Based on Akaike information criterion (AIC) (CS Table 64), the company selected the multinomial logistic regression including treatment and prior health state in its base-case. Regression parameters and transition matrices are presented in CS Tables 65–67

4.2.6.1.2 CKD state transitions

CKD progression (eGFR decline) was modelled using linear regression with covariates:

- uPCR category (uPCR <1.0 g/g, uPCR 1.0 - 3.0 g/g, uPCR >3 g/g)
- Treatment (pegcetacoplan, no pegcetacoplan)
- Age
- Sex

The company's base-case model included treatment and uPCR category (statistical fit not shown in CS Section 3.3). Regression parameters (eGFR decline per uPCR category, by treatment) and resulting transition matrices are presented in CS Tables 70–73. For patients with uPCR <1.0 g/g on pegcetacoplan + SoC, the model predicted an increase in eGFR. As this was considered clinically implausible, the company assumed no change in eGFR in this subgroup (CS Table 71).

4.2.6.1.3 Transitions to dialysis and transplants

Patients reaching CKD stage 5 were assumed to start dialysis in the next model cycle, with 88% commencing haemodialysis and 12% peritoneal dialysis, based on UKRR data.¹⁵ From stage 5 or dialysis, patients had a 13% probability per 3 months (derived from the RaDaR registry) to undergo

kidney transplantation (either from the CKD stage 5 or dialysis health state), which corresponds to a median time from dialysis initiation to transplant of 14.4 months (CS Table 74). This probability was assumed constant across first and subsequent transplants, and 17% of patients were assumed unsuitable for transplant and remained on dialysis for the remainder of their life.¹⁶ Graft survival in the first post-transplant cycle was set at 95%.¹⁷ The post-transplant CKD distribution (different from baseline) is reported in CS Table 75, with patients assumed to return to the baseline uPCR distribution (CS Table 61).

4.2.6.2 Relative effectiveness pegcetacoplan + SoC versus iptacopan + SoC

Currently iptacopan + SoC is not considered a relevant comparator, hence Section 4.2.6.2 (below) might be obsolete. However, for completeness the company's approach to incorporate the relative effectiveness pegcetacoplan + SoC versus iptacopan + SoC is summarised below.

4.2.6.2.1 uPCR state transitions

The relative effectiveness of pegcetacoplan + SoC versus iptacopan + SoC for uPCR was informed by a Bucher indirect comparison, generating an odds ratio (OR) of [REDACTED] (CS Table 68). This was applied to pegcetacoplan + SoC probabilities of transition to uPCR <1.0 g/g. Probabilities of transitioning to uPCR 1.0–3.0 and >3.0 g/g were calculated as the complement of the probability of achieving uPCR <1.0, proportionally allocated using the original pegcetacoplan + SoC transition weights to these states (CS Table 69).

4.2.6.2.2 CKD state transitions

The rate of eGFR decline (to inform CKD state transitions) for iptacopan + SoC was assumed to be the same as for pegcetacoplan + SoC, conditional on the corresponding uPCR level.

4.2.6.3 Assumptions related to disease progression

4.2.6.3.1 Stable disease

The company introduced a “stable disease” health state, based on Caravaca-Fontán (2020),¹⁸ a retrospective cohort study of 97 patients with C3G, across 39 nephrology centres in Spain, treated with MMF and corticosteroids. In that study, remission was defined either as “complete remission” (normalisation of eGFR and proteinuria) or “partial remission” (significant reduction in proteinuria with stabilised or improved eGFR). Approximately half (47%; 19% complete and 29% partial remission) of patients achieved remission after a median of 14 months, although one-third of these responders relapsed following treatment discontinuation (median time to relapse of 26 months, inter quartile range (IQR): 15–79 months).

In the company's model, stable disease was defined as a uPCR <0.5 g/g. This was calculated based on 26 weeks for the placebo group and 52 weeks for the pegcetacoplan group in the VALIANT trial. Subsequently, the calculated number of patients with stable disease was used to calculate the treatment specific 3-monthly probability of disease stabilisation (CS Table 76). For iptacopan + SoC the OR of [REDACTED] (CS Table 68) related to uPCR state transitions, was applied to the pegcetacoplan + SoC probability of disease stabilisation. Patients in stable disease were assumed not to experience CKD progression or eGFR decline.

The duration of stable disease was informed by Caravaca-Fontán (2020),¹⁸ assuming a constant relapse risk across all treatments with a median time to relapse of 26 months, resulting in a 3-monthly relapse probability of 7.7% (CS Table 77).

4.2.6.3.2 *Extrapolation and potential waning of treatment effect*

The base-case assumed no waning of relative treatment effect, i.e., a constant pegcetacoplan + SoC treatment effect over a patient's lifetime. This was justified by the company based on the VALIANT trial and the mechanism of C3 inhibition.

4.2.6.4 *Assumptions related to additional benefits*

4.2.6.4.1 *Impact on CV events*

The company assumed deviation from normal eGFR (~90 mL/min/1.73m²) increased the risk of CV events.¹⁹ The company included four CV events: stroke²⁰, heart failure²¹, CV mortality,²² and myocardial infarction²³ (CS Table 78). Age dependent (5-yearly age groups) probabilities of CV events per 3 months, for the general population, are reported in CS Table 79. No adjustments were made for probabilities of subsequent CV events (e.g., risk of recurrent stroke). Subsequently, the increase in risk of CV events according to CKD stage (compared with the general population) was sourced from a meta-analysis of individual participant data including 637,315 individuals without a history of cardiovascular disease from 24 cohorts included in the Chronic Kidney Disease Prognosis Consortium (CS Table 80)¹⁹.

4.2.6.4.2 *Impact of CKD on mortality*

General population mortality rates were obtained from Office for National Statistics (ONS) 2021–2023 life tables.¹⁵ Additional mortality risk by CKD stage was applied via hazard ratios (HRs) (CS Table 81).

EAG comment: The main concerns of the EAG relate to: a) 26-week placebo data and 52-week pegcetacoplan data from VALIANT were used in the model base-case, b) only using two (no intermediate) measurement points; c) the use of two separate regression models, d) regression diagnostics, e) assumption of identical transition probabilities pre- and post-transplant, f) stable disease assumptions, g) lack of exploring treatment effect waning, h) assumptions related to the addition of CV events, i) impact of CKD on mortality, j) relative effectiveness versus iptacopan.

- a) In the CS base-case, baseline and 26 weeks data (i.e., the randomised controlled period) were used to inform SoC while for pegcetacoplan + SoC baseline and 52 weeks data were used (i.e., the randomised controlled period + the open-label period; see CS Figure 5). This allows for more time for improvement (or regression to the mean) for pegcetacoplan + SoC compared with SoC only. Specifically, because the SoC arm was truncated at 26 weeks while the pegcetacoplan arm used 52 weeks of data, the latter allows more time for natural regression to the mean and spontaneous improvement to be captured, potentially exaggerating the apparent treatment effect. This asymmetry may bias treatment effect estimates by inflating the estimated benefit, as differences due to unequal follow-up are attributed to treatment. Hence, the EAG would have preferred to use baseline and 26 weeks data for both pegcetacoplan + SoC and SoC.
- b) To inform treatment effectiveness based on the VALIANT trial, only two measurement points were used (baseline and either 26/52 week data, no intermediate). The company suggested that assessing long-term, durable changes (instead of focusing on short-term changes) from baseline is preferred for examining clinical effectiveness. However, for informing cost effectiveness modelling, these assessments can hide transient but clinically relevant intermediate changes (e.g., temporary

worsening or improvement) that may influence estimated outcomes as well as long-term extrapolation. It is important to examine temporal patterns in the data to understand underlying disease dynamics. The company's approach may obscure short-term but clinically relevant changes, potentially misrepresenting the true pattern of disease dynamics over time. Unfortunately, the company did not respond to the clarification question (B12c and B20b) inquiring about the implications of this approach. The EAG believes the company's approach is suboptimal, in terms of use of already scarce data and might hide important variation over time.

- c) The CS base-case combines two regression models to inform treatment effectiveness: a multinomial logistic regression model for uPCR state transition (CS Table 65) and a linear model for eGFR decline including a uPCR covariate (CS Table 70). It is unclear to the EAG (and not justified in the CS) why two linked regressions were used rather than a parsimonious single model that simultaneously captures uPCR and eGFR (e.g., a multinomial logistic regression for uPCR state transitions with eGFR decline as a covariate). Moreover, given that both regression models include a treatment covariate, the CS base-case approach risks double-counting; part of the treatment effect on eGFR that operates through improvements in uPCR may have been counted twice (first via the uPCR model and again via the eGFR model) thus inflating the estimated overall effect of pegcetacoplan + SoC. Unfortunately, the company did not respond to clarification question B11 regarding justification for this approach nor were the requested scenario analyses (using one regression model) provided.
- d) The company provided further details regarding the estimated regression models. These were provided in response to clarification question B9 for the multinomial logit model to estimate uPCR state transitions (specifically clarification response Tables 24-26). Given the very large standard errors for several transitions (e.g., $>100\times$ larger for transitions to the uPCR >3 g/g health state than for the other covariates), the very low number of observations (or even none) for the transitions to and from the uPCR >3 g/g category and moderate overall model accuracy ($\approx 70\%$, indicating that the uPCR category is misclassified in 30% of cases), the EAG considers the multinomial model to have poor validity for estimating uPCR transitions.

Further details regarding the regression model used to estimate CKD state transitions was provided in response to clarification question B10. Given the inclusion of the uPCR categories, it is assumed that the rate of eGFR decline depends on uPCR level. Considering the figures provided in response to clarification question B10d (mean eGFR (change) over time, per treatment), this assumption does not seem to be supported by VALIANT trial data. This is also illustrated by clarification response Figures 8 and 9 comparing eGFR regression estimated by the regression model and observed in the VALIANT trial, indicating that the former does not seem consistent with trial data. Also, the regression model predicted an increase in eGFR (for patients with uPCR <1.0 g/g on pegcetacoplan + SoC), which was considered clinically implausible (and hence set no change in eGFR in this subgroup), which illustrates the limited clinical validity of this regression model. Given the discrepancy between the VALIANT data and model predictions, and the limited face validity of predicted eGFR improvements, the EAG considers the linear regression model used to estimate eGFR decline to be of limited credibility. Additionally, the treatment covariate that was included as a (non-significant) covariate in this regression model for eGFR was not properly justified. As argued above as well as indicated by the company (response to clarification question B13), this might induce double counting the treatment effectiveness of pegcetacoplan + SoC. Hence, the EAG prefers to exclude the treatment covariate for the regression model for eGFR in its base-case.

Given the above, both regression models, which are the fundament to estimate effectiveness in the health economic model, have limited credibility and (face) validity. Hence, potentially simpler approaches, such as the model structure used in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy), would have been preferred.

- e) The CS assumes identical transition probabilities pre- and post-transplant, justified by the limited availability of post-transplant data regarding changes in uPCR (clarification response B14a). This assumption might not be clinically plausible as (according to clinical feedback received by the company, clarification response B14a), transplanted kidneys tend to deteriorate more rapidly than native kidneys, since patients have only half the normal nephron mass and are exposed to nephrotoxic immunosuppressive medications that can further accelerate decline. Thus, the assumption of identical pre- and post-transplant transition probabilities lacks clinical plausibility and was unfortunately not explored by the company in scenario analyses (clarification response B14b). A simpler approach (i.e., a single post-transplant health state) for the post-transplant phase as used in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy) would have been preferred and might have allowed the use of external post-transplant data.
- f) The company included a 'stable disease' health state, defined as a uPCR <0.5 g/g. The EAG asked clarification (question B15) regarding the necessity, definition, implementation and impact of the 'stable disease' health state. According to the EAG, given that the CS base-case already is categorising patients into uPCR categories, modelling 'stable disease' appears to be redundant. The company's justification (clarification response B15a) conflates biochemical response (low uPCR) with the concept of durable remission or treatment discontinuation. While clinicians may consider monitored treatment discontinuation in selected diseases, no supporting evidence was provided that such practice is established or appropriate in C3G. According to the EAG clinical expert, there are no longitudinal studies that confirm remission in patients with C3G. Hence, the inclusion of a 'stable disease' state lacks empirical support. The 'stable disease' state appears redundant given existing uPCR categories and functions primarily as a treatment discontinuation mechanism rather than a distinct clinical state. The necessity and validity of including this health state remain unsubstantiated. Moreover, the specific implementation has a substantial impact on the cost effectiveness results. The following alternative assumptions have a substantial impact (see clarification response B15): i) an alternative stable disease category (e.g. uPCR <1.0 g/g), ii) shorter duration of stable disease (e.g., 12 months), as well as iii) assuming no treatment discontinuation in stable disease. Given the above, the EAG prefers to exclude the 'stable disease' health state in its base-case, i.e., by setting the transition probabilities to this health state to zero.
- g) The company assumed no treatment effect waning. Evidence and scenario analyses were requested by the EAG regarding the assumption of a constant pegcetacoplan treatment effect. This was a similar assumption as in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy) and assuming no treatment effect waning was consistent with the clinical expert opinion obtained by the EAG. The company argued that based on the well-understood mode of action of pegcetacoplan (blocking overactivation of the alternative pathway and reducing C3 deposition in the glomeruli), experts concluded there is no scientific rationale to expect the pharmacological effect of pegcetacoplan to wane over time. While the assumption of no treatment waning appears reasonable, it would have been informative to explore the impact of treatment waning, including the scenario analyses requested in clarification question B16c as well as for instance assuming reduced treatment effect post-transplant.
- h) The CS base-case included the assumption that deviation from normal eGFR (~90 mL/min/1.73m²) increased the risk of CV events. Justification and supporting evidence were requested by the EAG for including CV events in the CS base-case (Clarification question B17). Unfortunately, no detailed responses were provided by the company. The EAG noted that in the CS of GID-TA11331 (iptacopan for treating complement 3 glomerulopathy), it was stated that *"Since no data could be identified on the risk of cardiovascular (CV) events in patients with C3G and clinicians considered that literature from CKD more broadly may overestimate the incidence of CV events, CV events were included in a scenario analysis only"*. Moreover, the EAG's clinical expert stated that *"CKD*

and subsequent kidney failure associates with cardiovascular risk and mortality. Pegcetacoplan might benefit patients by delaying or preventing progression of CKD rather than any direct effect of pegcetacoplan on cardiovascular risk of mortality associated with CKD". Given the above, the EAG excluded CV events from its base-case.

- i) The CS base-case included the impact of CKD on mortality. Clarification and justification were requested by the EAG related to the HRs applied for CKD-related mortality, to ensure consistency with trial/external data and prior NICE appraisals. The HRs applied in the original CS base-case appear to be higher than those reported in prior NICE TAs and external literature. For instance, in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy) the HR was 1.32 for CKD stages 1-4 and 3.99 for CKD stage 5 as well as on dialysis and post-transplant. Following clarification, the company revised its base-case to apply HRs more consistent with GID-TA11331 (clarification response Table 56: 1.00, 1.11, 1.88, 3.01, 4.26 for CKD stages 1–5).
- j) CS Section 3.3.2 describes the inclusion of the relative treatment effect versus iptacopan + SoC through applying an OR of [REDACTED] for uPCR (CS Table 68 provides results of Bucher's indirect comparison between pegcetacoplan and iptacopan for proteinuria-related outcomes [24h versus 24h]). The EAG noted that the OR of [REDACTED] applied in the model was different than those reported in CS Section 2.10 (on indirect and mixed treatment comparisons). According to the company, this OR was based on analyses using consistent methods of proteinuria estimation (24-hour collections in both trials), whereas Section 2.10 reported ORs derived from each trial's primary assessment method (FMU in VALIANT, 24-hour in APPEAR-C3G). Based on clarification responses to question B13, several notable differences in population (VALIANT versus APPEAR-C3G) and potential imbalances in effect modifiers, that might affect the abovementioned OR estimated through the Bucher method, cannot be fully excluded. Moreover, the indirect comparison conducted by the company was stratified per uPCR category. Only the OR of [REDACTED] for the <1 (g/g) category (that favoured pegcetacoplan + SoC) was used in the CS base-case, while the ORs [REDACTED] and [REDACTED] for the ≥3 (g/g) and 1-3 (g/g) categories (that favoured iptacopan + SoC) were not included. Consequently, the EAG considers the indirect comparison not implemented conservatively, as only the OR favouring pegcetacoplan was applied. Therefore, the EAG would have preferred if the company explored the impact of using different OR, for instance the OR of [REDACTED] reported for the ≥50% uPCR reduction category in a scenario analysis. However, given that iptacopan + SoC is currently not considered a relevant comparator in this appraisal, this issue is obsolete.

4.2.7 Adverse events

In CS Section 3.3.7, the company stated that adverse events were not considered in the economic modelling because the number of serious TEAEs in each VALIANT treatment arm during its randomised controlled period was limited to six, affecting <5% of the trial population. Nevertheless, in CS Sections 3.4.5 and 3.5.5, disutilities and costs were assigned to adverse reactions due to cardiovascular (CV) events. The probability of each CV event to occur was informed by a meta-analysis¹⁹ comprising of, but not exclusive to the general CKD population, featuring a mean age of 47 years.

EAG comment: The main concerns of the EAG relate to: a) exclusion of AEs besides CV events, b) inclusion of CV events.

- a) The company did not include AEs besides CV events in their economic model. However, the CS reported TEAEs occurring in VALIANT. In the RCT, repeated occurrence of identically categorised AEs was counted once for the affected patient, hindering an event-based assessment (Response B19,³ Section 9.7.2.1²⁴). The findings of VALIANT were not cross validated via a

SLR on published evidence as well as TAs, despite the EAG's request³. The company did also not provide an updated health economic model with scenario analyses using such event-based AE incidences (exploring thresholds of 0%, $\geq 5\%$) and different AE severity (all grades, grade ≥ 3). Based on the current CS classification accessible to the EAG, the external EAG clinical expert perceived AE occurrence in VALIANT as balanced and reflective of clinical practice. He expected an increased risk of local skin reactions for pegcetacoplan, and of infections due to encapsulated organisms for both pegcetacoplan and iptacoplan. Although not reported in the pegcetacoplan and iptacoplan trials, the EAG clinical expert stated that conventional immunosuppression medications (e.g. mycophenolate mofetil, prednisolone) are subject to well-documented side effects. Furthermore, the EAG has little insights into AEs apparent in later stages in the CS patient population, which were potentially not captured within VALIANT. Although requested, the company did not provide a corresponding SLR, citing time constraints. It referred to the inclusion of CV events and expected little impact on model results due to observed similarity of AEs incidences across treatments.

Considering the above, the EAG criticises that adverse events are not sufficiently assessed nor incorporated in the health economic model. Although the EAG expects the impact on cost effectiveness to be minimal, the company should provide the cross-validation and analyses requested during clarification.

- b) The CS captures the relationship between worsening kidney function (as patients deteriorate with CKD stages) and an increased risk for CV events, although specific evidence is limited for C3G and primary IC-MPGN³ and no CV events were reported in VALIANT. Therefore, the company informed CV occurrence probabilities and disutilities by literature from the broader CKD population and beyond. Upon the request of the EAG, the company confirmed that in generally younger C3G patients CV events are likely less common and that sourced values may be overestimates³. Hence, the EAG deems the sourced input values as inappropriate for the CS patient population, and in line with the reasoning laid out in EAG comment h) on the risk of CV events, Section 4.2.6, the EAG decided to exclude CV events, corresponding disutilities and costs in the EAG base-case.

4.2.8 Health-related quality of life

The health state utility values (HSUVs) applied in the CS were informed by the VALIANT pivotal trial and literature.

4.2.8.1 Health-related quality of life data identified in the literature review

An SLR on HSUV data for the C3G and IC-MPGN population was performed in 2024 with a cut-off date of 2014 and updated in August 2025. Two abstracts were identified, both analysing ADELPHI C3G Disease Specific Programme (DSP) data^{25, 26}. Sidhu et al.'s study (2024) reported European Quality of Life-5 Dimension-5 Levels (EQ-5D-5L)-based descriptive HSUVs for C3G-specific CKD stages 1 to 4/5.²⁶ The values were mapped using the US tariff and were derived from a total of 100 patients, including some from the UK. Furthermore, three TAs in glomerular diseases²⁷⁻²⁹ were cited which used Cooper et al. (2020)³⁰, an SLR on the wider CKD, to inform HSUVs (including HSUVs for patients undergoing haemodialysis or peritoneal dialysis).

4.2.8.2 Health state utility values

The VALIANT clinical trial informed utility values for the pooled CKD stages 1 and 2, using EQ-5D-5L data from baseline, week 26 and 52, i.e., including the open label period (featuring patient cross-over to pegcetacoplan). It was mapped to EQ-5D-3L with the Decision Support Unit algorithm provided

in the “eq5d” R package.³¹⁻³³ The impact of covariates on EQ-5D-3L was explored in linear regression models, with baseline EQ-5D, age, and uPCR levels >1g/g being included in the final model. CKD stages 3 to 5 were informed by Sidhu et al.’s study (2024).²⁶ The utility decrement identified in VALIANT for uPCR levels >1g/g was applied to CKD stage 3 to 5 utilities for health states with uPCR levels >1g/g¹. Cooper et. al (2020) informed HSUVs for patients undergoing haemodialysis (HD) or peritoneal dialysis (PD).³⁰ No HSUVs for patients receiving a peri-operative transplant could be retrieved from the VALIANT trial or literature, hence the same HSUV as for HD was assumed (i.e., the lower one of the dialysis HSUVs). After transplant, patients return to the same HSUVs as pre-transplant patients. Age- and gender-adjusted general population utilities were used to capture the decline in health over time.³⁴

Due to the small sample size, implausible HSUVs and use of EQ-5D-5L with the US tariff in ADELPHI DSP²⁶ used in the CS base-case, the company provided a scenario with Cooper et al. (2020)³⁰ informing CKD stage 3 to 5 utilities.

A summary of all HSUV used in the cost effectiveness analysis is provided in Table 4.4.

Table 4.4: Health state utility values

Health state		Utility value	Reference
CKD 1, 2	Remission	0.91	VALIANT
	uPCR <1 g/g	0.91	
	uPCR 1 g/g-3 g/g	0.84	
	uPCR >3 g/g	0.84	
CKD 3	Remission	0.75	Sidhu et al. 2024
	uPCR <1 g/g	0.75	
	uPCR 1 g/g-3 g/g	0.69	Sidhu et al. 2024, VALIANT (uPCR disutility applied)
	uPCR >3 g/g	0.69	
CKD 4, 5	Remission	0.58	Sidhu et al. 2024
	uPCR <1 g/g	0.58	
	uPCR 1 g/g-3 g/g	0.52	Sidhu et al. 2024, VALIANT (uPCR disutility applied)
	uPCR >3 g/g	0.52	
HD	-	0.44	Cooper et al. 2020
PD	-	0.53	Cooper et al. 2020
Undergoing transplant	-	0.44	Cooper et al. 2020 (assumption: same as HD utility)
Based on CS Table 85			
CKD = chronic kidney disease; CS = company submission; g/g = grams of protein per gram of creatinine; HD = haemodialysis; PD = peritoneal dialysis; uPCR = urinary protein to creatinine ratio			

4.2.8.3 Disutility values

Cardiovascular event-related disutilities, i.e., myocardial infarction, heart failure and stroke, were applied as a one-off decrement for patients experiencing that event per cycle. They were assumed to be of one cycle duration and informed by literature.³⁵⁻³⁷

EAG comment: The main concerns of the EAG relate to: a) validity of the VALIANT HRQoL data, b) the regression analysis of VALIANT trial data to inform CKD stages 1-2 utilities in the health

economic model, c) the source and adjustment of utility values for CKD stages 3-5, d) lack of alignment of literature-based utility values for dialysis (HD, PD) and transplant with the CS patient population, e) (lack of) inclusion of disutilities.

- a) VALIANT HRQoL data measured at baseline, week 26 and 52, the latter representing the open-label period, informed CKD stage 1 and 2 utilities but not advanced CKD stages due to little data.

First, the few, spread-out measurement points could fall short to capture the impact of disease progression, with the EAG clinical expert anticipating changes in HRQoL over weeks and months due to proteinuria and the reversal of nephrotic syndrome (see Appendix). Please see EAG comment b) in Section 4.2.6. for further details.

Second, these few measurements in a small study population seem to have led to implausible findings, questioning VALIANT's appropriateness to address the CS decision problem; the EAG noted the company's assessment that *"utility values for CKD stages 1–2 in VALIANT were higher than those reported in the literature and even exceeded those of the UK general population"*.³ The company attributed this to good health of study participants.

Third, Table 64 of the CS clarification response³ stratifying utility values by CKD stage (up to CKD stage 4), indication and age group suggests that addressing subgroups separately could be of added value for the CS decision problem (see EAG comment a) in Section 4.2.3). It showed considerable differences for some CKD stages between adults versus adolescents, as well as C3G versus IC-MPGN. Paediatric clinicians consulted by the company emphasised that the disease would impact adolescents more, especially if in dialysis.³ However, its clinical experts expected the difference between adults and adolescents to be non-significant. The EAG does unfortunately not have insight on how these utilities have been derived and was further concerned about partly implausible increases in utility values despite progression, simultaneously acknowledging that there might be few observations in some of these groups.

- b) The EAG identified various issue related to the methods to inform CKD stage 1 and 2 utility values from VALIANT. First, the CS used pooled VALIANT HRQoL data to inform CKD stage 1 and 2 jointly and thus differentiated only between uPCR levels lower or higher than 1g/g. This results in a mismatch with the health economic model structure with regard to uPCR thresholds as well as CKD stage differentiation. It remains unclear to the EAG whether HRQoL data from patients with CKD stages 3 and 4 were excluded in the subsequent regression analyses. The EAG clinical expert deemed CKD stages 1 and 2 very mild and pooling them as reasonable. He considered the impact of disease activity due to complement activation in C3G and proteinuria to be more important. What is more, clinical experts consulted by the company identified a uPCR level of >3g/g as an important indicator for significant HRQoL decrease across all CKD stages,³⁸ contrary to the CS cut-off at 1 g/g which was applied both to VALIANT and literature-sourced utility values.

Second, although there was considerable missingness of data in VALIANT (CQ response B21.a³), no corresponding missing data assessment (e.g., missing data patterns and mechanisms)³⁹ nor imputation was performed. The EAG further has no information on missing data of independent variables considered for regression analyses. The EAG considers a thorough assessment on missingness central to inform appropriate imputation techniques. It would have appreciated a scenario analysis with HRQoL regression analyses informed by imputed data.

Third, the company utilised linear regression, which does not account for repeated measures within individuals. Upon clarification, the company provided evidence which suggested that the linearity assumption was not violated but the normality assumption was, although visual

representation supporting these statements was lacking. It provided additional analyses exploring MMRM with different variance-covariance structures, however not clearly specifying the random parts nor adding fixed time effects. Those MMRMs showed a better statistical fit although with no significant changes in estimates according to the company. It also explored additional covariates such as type of disease (C3G versus IC-MPGN), transplant status, and CKD stage, yet stayed with uPCR levels >1g/g and age utilised in the CS base-case. However, due to time constraints, the company kept linear regression estimates in its base-case. Whereas the EAG agrees that estimates seem similar, it is apprehensive of the age covariate being non-significant and the uPCR >1g/g disutility being smaller in the best fitting MMRM featuring a simple variance-covariance matrix structure. In any case, it would like to see these analyses replicated and extended⁴⁰ for the regression model which is aligned with the CS health economic model structure.

Finally, the EAG further criticises the company's lack of using the standard errors derived from the HRQoL regression analyses to inform uncertainty analyses. Instead, the CS used 20% of the deterministic value as the standard error. Overall, the company should align the HRQoL regression model structure with the CS health economic model structure and clinical expert opinion. Further, the EAG advises a more in-depth assessment and subsequent imputation of missing data, the use of more advanced regression model techniques as well as full inclusion of findings such as standard errors in the health economic model. The EAG considers these deviations from good practice a key issue.

- c) Due to limited data availability in VALIANT, CKD stages 3 to 5 were informed by literature, namely ADELPHI DSP data on C3G.²⁶ There was no differentiation between uPCR levels, resulting in a mismatch with the CS model structure. Whereas the EAG appreciates the company's effort to align literature-based values with the model structure and clinical expert feedback stating that uPCR levels >3g/g would be accompanied by a distinct drop in HRQoL across CKD stages,³⁸ it is concerned about the risk of misalignment with clinical expert feedback and double counting in the chosen approach: The company applied a utility decrement (-0.063) identified in VALIANT for uPCR levels >1 g/g (not >3 g/g) also to ADELPHI DSP utilities, i.e., to health states where CKD stage 3 to 5 coincide with artificially imposed uPCR levels >1 g/g. Therefore, the EAG base-case does not apply this decrement.

ADELPHI DSP, a cross-sectional survey, was prone to multiple shortcomings, namely lack of IC-MPGN patients, small sample size (in total, 100 patients filled out an EQ-5D-5L survey, and 15 patients informed a joint CKD stage 4 and 5), inclusion of non-UK patients, the use of EQ-5D-5L and US tariff and not EQ-5D-3L as stipulated by NICE guidance and unexpectedly increasing values for CDK stages 1-3A. Although the APPEAR C3G randomised controlled trial, the main source of evidence in GID-TA11331,¹³ only addressed C3G and had fewer (N=74) patients and few UK patients, its EQ-5D-5L estimates sourced from eight observation points over one year (providing 484 observations) featuring low missingness (9%) were mapped to EQ-5D-3L using a UK value set.^{13, 41} A total of 16 observations were reported for CKD stage 4.¹³ Therefore, the EAG preferred to inform CKD stages 3 and 4 in its base-case by APPEAR C3G,¹³ and CKD stage 5 by the age- and gender-adjusted value from Jesky et al. (2016)⁴² as in GID-TA11331 (i.e., CKD stage 3: 0.86, CKD stage 4: 0.85, CKD stage 5: 0.73 adjusted to 0.81).¹³ This proved in line with clinical expert feedback, showing a distinct “step-down from CKD 4 to 5”,³⁸ not mirrored in the CS base-case. However, the EAG acknowledges the limitations of this approach, and also conveys to the committee that the majority of the six experts consulted by the company stated that CKD stage 4 and 5 utilities should be lower than 0.74 and 0.73, respectively.³⁸ This is in part contrary to prior NICE TAs (Table 65³). A “potential for more rapid loss of kidney function, sometimes progressing to ESKD at a younger

age, recurrent flares and ongoing inflammation, and higher levels of fatigue” was expected.³

In the CS base-case, the study population was not adjusted for age and gender to match the CS patient population. However, CS scenario analysis 5 addressed this limitation with regard to age yet not gender. Unfortunately, the EAG was unable to also apply this adjustment to other literature-based values in the health economic model and hence assumed that utility values taken from GID-TA11331 address the CS modelled patient population sufficiently. In future analyses, the EAG would appreciate if this limitation was solved by the company to facilitate alignment of literature-based utilities considering age and gender with the CS decision problem.

- d) Utility values for dialysis (HD, PD) were sourced from the SLR by Cooper et al.,³⁰ which reported utility values from Lee et al.⁴³ The utility of undergoing transplant was assumed equivalent to HD. The EAG is concerned that they are inappropriate due to differences in the patient populations (Lee et al.: general UK CKD population; 59% male; mean age: 58 (males), 56 (females)) featuring different risks of comorbidities which have not been adjusted for in the CS. Therefore, the EAG used Lee et al.’s⁴³ age- and gender-adjusted values from GID-TA11331¹³ as these at least address the C3G population (i.e., HD: 0.49; PD: 0.58) and are aligned with CKD stages 3-5 utilities.

Regarding the utility value of undergoing transplant, the EAG requested a separate SLR to assess the assumption of equivalence with HD. The company did not provide this, citing time constraints. The EAG clinical expert perceived the company’s approach to use the lowest utility value as reasonable but stressed that after successful transplant patients would revert to health states comparable to non-transplant patients depending on CKD stage and uPCR. As this health state applies only for one model cycle, the impact on cost effectiveness is expected to be minor. Thus, the EAG followed this assumption in the EAG base-case.

- e) The CS does not reflect deterioration of patients due to treatment-emergent adverse events, which the EAG views as a limitation (see EAG comment a) in Section 4.2.7.). Furthermore, the EAG decided to exclude disutilities related to cardiovascular events in its base-case, please see EAG comment b) in Section 4.2.7. for justification.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, health state costs (healthcare resource utilisation (HCRU): disease monitoring, transplant, and dialysis costs), opportunity costs of saved kidneys, and event costs for end of life and cardiovascular events.

Where available, unit prices were based on the National Schedule of NHS costs (2023-24),⁴⁴ the 2023/2024 drugs and pharmaceutical electronic market information tool (eMIT),⁴⁵ the 2023 Unit Costs of Health and Social Care (Personal Social Services Research Unit, PSSRU),⁴⁶ and the British National Formulary (BNF).⁴⁷ Where unavailable, unit prices were sourced from literature.

4.2.9.1 Resource use and costs data identified in the literature review

According to the CS, relevant cost and HCRU data for patients with C3G or primary IC-MPGN was captured in the SLR (CS Section 3.1). No studies reporting on costs and two studies reporting on HCRU were identified. It was not mentioned whether these were used to inform the economic model.

4.2.9.2 Treatment costs (with PAS)

Treatment costs were assigned per 3-month model cycle, corresponding to 13.04 weeks. For the intervention, costs of the subcutaneously administered pegcetacoplan in addition to SoC applied. No

pegcetacoplan administration costs were modelled, as it was assumed to be self-administered by patients. Patients in the comparator arm incurred the costs of iptacopan in addition to SoC, or SoC therapies only. Iptacopan and SoC therapies are given orally, hence the company assumed no administration costs. No pack or vial sharing was considered in the model.

For intervention and comparator acquisition costs, 100% adherence was assumed, except for:

- Patient treatment discontinuation for pegcetacoplan or iptacopan due to safety concerns, as per VALIANT estimated as a [REDACTED] per-cycle discontinuation rate, or due to entering CKD stage 5 or dialysis (CS Section 3.3.6)
- Patient improvement to an assumed point of stable disease, i.e., uPCR <1 g/g (CS Section 3.3.3).

Pegcetacoplan

The CS detailed a list price of pegcetacoplan of £3,100 per 1,080mg/20ml vial. Administered twice weekly, the acquisition costs amounted to a cost per model cycle of £80,876.79. Taking into account the patient access scheme (PAS) discount, the per model cycle cost was [REDACTED].

Standard of care

For C3G and IC-MPGN, the company defined a SoC basket including ACEi and/or ARBs, immunosuppressants, systemic corticosteroids, and SGLT2 inhibitors as treatment categories. The randomised period of the VALIANT trial informed the relative use of each category, incorporating the medication shares within each category yet not those medications administered in fewer than two study participants. For example, in the treatment category of immunosuppressants, the medications mycophenolate and tacrolimus (among others) were accounted for relative to their use, but ciclosporin was excluded due to small occurrence. The maximum daily dose was used to approximate daily medication needs. Daily use was valued in the base-case via an even share of formulation assumption, i.e., for each treatment category an average price of the applicable, different treatments was calculated (for these treatments, disregarding pack sizes and strength, expressed in dose per unit). The average (“equal split”) costs per treatment category were adjusted for the model cycle length and multiplied by the shares identified in VALIANT.

Iptacopan

In the CS, the list price per 56 capsule pack (200 mg per capsule) was £26,500. Iptacopan is administered twice daily, amounting to £86,420.76 per model cycle.

Subsequent treatment

Post transplantation, the company assumed that patients continued their treatment (i.e., pegcetacoplan, SoC alone or iptacopan + SoC), except patients in the stable disease health state.

4.2.9.3 Health state costs

Health state costs reflect HCRU for disease monitoring as well as transplant and dialysis costs. Health state costs are presented in Table 4.5.

CKD stage and uPCR level health state costs

Disease monitoring costs included nephrologist outpatient visits, nurse visits, inpatient visits, and blood tests. As per the CS, costs were estimated using a micro-costing approach, where clinical expert input

informed expected average annual HCRU for each CKD/uPCR health state (CS Table 87). HCRU was valued with unit costs from the NHS national cost collection (ref) and subsequently adjusted to the model cycle length. Due to uncertainty associated with expert elicitation of healthcare resource utilisation data, a scenario analysis was conducted using values from previous NICE STAs: TA1074 and TA937.^{27, 28}

Dialysis health state costs

The CS assumed three times weekly haemodialysis and daily peritoneal dialysis. Dialysis unit costs were derived from the NHS Schedule of Reference Costs. As the company deemed several healthcare resource groups from the Schedule relevant, these were combined and weighted with activity-based patient distribution data.

Moreover, the company assigned a one-off cost to patients entering the dialysis health state to capture costs related to e.g., fistula creation or catheter insertion. It differentiated for haemodialysis and peritoneal dialysis, considering the respective distributions.

The HCRU and costs associated with (initiation of) dialysis per annum are presented in CS Table 89.

Transplant health state costs

Assessment prior and after transplant, as well as the surgery itself, was included as a one-off procedural cost of £19,827 (CS Table 90). The CS identified HCRU connected to maintenance, namely tacrolimus monotherapy (0.25 mg/kg), two nephrologist and general practitioner (GP) appointments each, accompanied by blood tests, and 0.5 hospitalisations per annum (CS Table 91). The NHS Schedule for reference costs and Personal Social Services Research Unit schedule was used for valuation.

Table 4.5: Health state costs

Health states		Cost per model cycle (£)
CKD 1 - 3	Remission	247.80
	uPCR <1 g/g	335.96
	uPCR 1 g/g-3 g/g	495.59
	uPCR >3 g/g	814.87
CKD 4	Remission	495.59
	uPCR <1 g/g	495.59
	uPCR 1 g/g-3 g/g	1,131.13
	uPCR >3 g/g	1,274.09
CKD 5	Remission	638.55
	uPCR <1 g/g	638.55
	uPCR 1 g/g-3 g/g	1,906.62
	uPCR >3 g/g	2,049.58
Haemodialysis	-	8,292.74
Peritoneal dialysis	-	9,663.08
Post-transplant	-	1,828.18
Source: CS Tables 88, 89, 91.		
CKD = chronic kidney disease; CS = company submission; g/g = grams of protein per gram of creatinine; uPCR = urinary protein to creatinine ratio		

4.2.9.4 Event costs

The company stated that no costs associated with adverse events were included. However, it considered costs related to cardiovascular events and mortality identified from literature^{46, 48} as relevant for the CS decision problem, and included them in the model as one-off costs at time of occurrence (CS Table 97).

4.2.9.5 Opportunity costs

The CS assumed pegcetacoplan to reduce kidney transplant demand in patients with C3G or IC-MPGN and incorporated this “opportunity cost of saved kidneys”. The cost savings of a transplanted kidney compared to dialysis was reported as £241,000 over a period of ten years.⁴⁹ Waiting time for a kidney transplant in the UK was captured by a queuing model.⁵⁰ For each transplant avoided, the average waiting time was reduced by 1.3 days. Scaled to the assumed annual number of 3,043 waiting patients, 10.65 years of QALY gains and cost savings applied according to the company and were incorporated in the CS base-case.

EAG comment: The main concerns of the EAG relate to: a) exclusion of pegcetacoplan administration costs; b) use of a constant discontinuation rate overtime; c) excluding drug wastage costs; d) exclusion of costs for vaccines and antibiotics.

- a) The CS does not include administration costs for pegcetacoplan, under the assumption that pegcetacoplan would be self-administered subcutaneously by all patients with use of a commercially available syringe system. CQ B25 requested justification and supporting evidence for assuming that: i) no patients would receive pegcetacoplan as administered by a healthcare professional, and ii) that the cost of the syringe system would not fall under the NHS and PSS perspective on costs. In response, the company suggest that those that initiate treatment are anticipated to receive initial training from a specialist nurse (assumed to be provided during a regular hospital appointment) with no additional administration costs for those that self-administer. The company assume, based on experiences in Paroxysmal Nocturnal Haemoglobinuria (PNH), that all patients will receive their first dose in clinic and self-administered subsequently. The company are not aware of any patient requiring administration in hospital, unless the patient is in hospital for another reason. However, the clinical expert consulted by the EAG suggested that, whilst they are aware of self-administration as an option, patients were administered in-centre during clinical trials the expert was involved in. Thus, the EAG remain unable to validate the company’s assumption. Further, the company suggest that the syringe system for self-administration will be company-funded, mitigating the need to include the associated cost in the economic model. The current approach therefore assumes that no additional time is required to administer pegcetacoplan in hospital during first visit nor for those receiving hospital-based administration when already in hospital. This is likely to underestimate the administration costs for pegcetacoplan. In response to CQ B25 d), which requested a scenario analysis incorporating administration costs for patients whose treatment would be administered by a healthcare professional and the cost associated with providing instructions to those that self-administer, the company include a one-off cost in the first cycle for patients upon initial dose and for home care for the second and third doses to check that patients are administering correctly. This approach does not account for hospital administrations required for patients in hospital for other reasons (other than for pegcetacoplan administration), nor any other hospital-based administrations. The EAG would like to see further evidence to support the assumption that all patients would receive the first dose within hospital, followed by self-administration. Further, supporting evidence regarding the proportion of patients that would receive doses in hospital due to being there for another reason

would be preferred. To fully assess the impact of this assumption, the EAG would like to see a scenario analysis which assumes all patients receive pegcetacoplan doses by a healthcare professional within a hospital setting.

- b) CS Section 3.3.6 highlights that a constant discontinuation rate of [REDACTED] per model cycle was assumed for pegcetacoplan +SoC and iptacopan +SoC (iptacopan +SoC due to lack of real-world data) based on the six patients that discontinued treatment during the VALIANT trial. The EAG requested justification and supporting evidence (CQ B26) for this assumption. Further, the EAG requested an updated economic model and scenario analyses (informed by external data, expert inputs, and/or other TA within chronic kidney disease) exploring alternative discontinuation rates and time-varying discontinuation rates. Time to treatment discontinuation analyses based on the VALIANT trial (including Kaplan-Meier analyses, parametric survival analyses, and exploring [cumulative] hazard overtime and other diagnostic plots consistent with NICE DSU TSD 14) were also requested to inform treatment discontinuation for pegcetacoplan +SoC, iptacopan +SoC, and SoC in an additional scenario analysis. The company express the constant discontinuation rate utilised was considered acceptable given the lack of data to inform long-term discontinuation rates in C3G/IC-MPGN patients and that the approach was in line with committee discussions during the iptacopan appraisal for C3G. The company provided results informing a constant discontinuation rate of 1.57% used in GID-TA11331. Time-to-treatment discontinuation analyses were also provided with the impact of the 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. The company acknowledged the limitations of using a simplified constant discontinuation rate in its clarification response, as several factors are likely to vary discontinuation over time (e.g., behavioural factors, accumulation of adverse events over time and fluctuations in symptoms). As such, the EAG questions whether a constant discontinuation rate is reflective of what would be expected in clinical practice. The EAG would prefer to see a scenario analysis as requested in their clarification letter incorporating time-varying discontinuation rates.
- c) Drug wastage and vial sharing were not clearly discussed within the CS. The EAG requested justification and supporting empirical evidence as to whether drug wastage and vial sharing are applicable to pegcetacoplan + SoC, iptacopan + SoC, and SoC. The 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. The EAG would prefer to see the analysis requested (i.e., per pack costing for oral treatments) as the current approach deviates from NICE guidance. Further, provided the company assume in its base-case that all patients would self-administer pegcetacoplan, this could result in higher wastage due to missed doses. As such, it remains unclear whether the current approach is indeed conservative.
- d) 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*. Further, as per the EAG-consulted 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. The 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. Furthermore, despite the EAG removing the stable disease health state from its base-case for the reasons provided in Sections 4.2.2 and 4.2.6, it considers a scenario analysis including the cost of biopsy upon entering stable disease to be informative.

4.2.10 Disease severity

Section 3.6 of the CS states that "*The technology is not expected to meet the criteria for a severity modifier*" with no QALY shortfall analysis seemingly conducted.

EAG Comment: The EAG accepts the company statement and has not applied a severity modifier in any of its analyses.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

The CS included base-case cost effectiveness results (probabilistic, including PAS) of pegcetacoplan + SoC compared to SoC alone and iptacoplan + SoC. Pegcetacoplan + SoC was more costly than SoC alone with incremental costs of [REDACTED], and less costly than iptacoplan + SoC with incremental costs of -[REDACTED]. Pegcetacoplan + SoC was more effective than SoC alone and iptacoplan + SoC with incremental QALYs of [REDACTED] and [REDACTED], respectively. This amounted to an ICER of £50,571 per QALY gained versus SoC alone and pegcetacoplan + SoC dominating iptacoplan + SoC (Table 5.1). The incremental net health benefit (iNHB) of pegcetacoplan + SoC versus SoC alone at willingness to pay (WTP) thresholds of £20,000 and £30,000 was [REDACTED] and [REDACTED]. Results of the fully incremental probabilistic analyses are provided in Table 5.1 below.

Table 5.1: Company submission pairwise probabilistic results of pegcetacoplan + SoC versus SoC alone and iptacoplan + SoC.

Treatment	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)	iNHB at £20,000	iNHB at £30,000
Pegcetacoplan + SoC	[REDACTED]	[REDACTED]	-	-	-	[REDACTED]	[REDACTED]
SoC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£50,571	[REDACTED]	[REDACTED]
Iptacoplan + SoC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant	[REDACTED]	[REDACTED]
ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life year; SoC = standard of care							

Overall, the technology is modelled to affect QALYs (deterministic) by:

- Increased time to disease progression with incremental QALYs gained in early CKD stages 1 and 2 of [REDACTED] versus SoC and [REDACTED] versus iptacoplan + SoC.

Overall, the technology is modelled to affect costs (deterministic, including PAS) by:

- Increased acquisition costs versus SoC with incremental costs of [REDACTED], and reduced acquisition costs versus iptacoplan + SoC with incremental costs of [REDACTED].
- Reduced dialysis and transplant costs with incremental costs of [REDACTED] versus SoC and [REDACTED] versus iptacoplan + SoC.

The modelling assumptions that have the greatest effect on the ICER are:

- Assuming treatment discontinuation in the stable disease health state. Removing treatment discontinuation in the stable disease health state in a scenario analysis increased the company ICER for pegcetacoplan + SoC to [REDACTED].
- The inclusion of a stable disease health state. Removing the stable disease health state in a scenario analysis increased the company ICER for pegcetacoplan + SoC to [REDACTED].
- The inclusion of cost savings and QALY gains associated with the reallocation of kidneys no longer required by patients treated with pegcetacoplan or iptacoplan. Removing these cost

savings and QALY benefits in a scenario analysis increased the company ICER for pegcetacoplan +SoC to [REDACTED].

EAG comment: The main concerns of the EAG relate to: a) cost effectiveness results of pegcetacoplan + SoC versus iptacoplan + SoC, and b) the company's updated base-case following clarification.

- a) Iptacoplan +SoC is no longer considered a relevant comparator within this appraisal. However, for completeness, the EAG has reported cost-effectiveness results from the CS including this comparator. Subsequent EAG analyses do not include iptacoplan +SoC as a comparator.
- b) In response to the clarification letter, the company updated its base-case (Table 5.2) including the following changes:
 - Assumption that at the time of the transplant, all patients have a uPCR <1.0 g/g. In the subsequent cycle, [REDACTED] of patients are assumed to be in the uPCR <1.0 g/g subgroup, and [REDACTED] in the uPCR 1.0-3.0 g/g health state.
 - Updated all-cause mortality HR from entire cohort in Darlington et al. (2021).⁵¹
 - Correction of an error in the range at which uPCR transitions were varied in the PSA.

Table 5.2: Updated company base-case: pairwise probabilistic results of pegcetacoplan + SoC versus SoC alone and iptacoplan + SoC.

Treatment	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)	iNHB at £20,000	iNHB at £30,000
Pegcetacoplan + SoC	[REDACTED]	[REDACTED]			-	[REDACTED]	[REDACTED]
SoC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£36,954	[REDACTED]	[REDACTED]
Iptacoplan +SoC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant	Dominant	Dominant

ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life year; SoC = standard of care

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses. The probabilistic CS base-case analyses indicated cost effectiveness probabilities of [REDACTED]% and [REDACTED]% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively. Versus SoC, the DSA showed that the results were most sensitive to changes related to pegcetacoplan (before transplant) disease remission probability per cycle from uPCR1 state and probability of disease relapse after remission per cycle. Versus iptacoplan + SoC, the DSA showed that the results were most sensitive to changes in utilities for remission CKD 1 and 3 health states. The company conducted several scenario analyses. The results showed ICERs ranging between £18,266 and £31,765 per QALY gained versus SoC. Pegcetacoplan was dominant versus iptacoplan in all scenarios. The three most influential scenarios that increased the ICER were: 1) Costs in the CKD/uPCR health states by CKD stage only (informed by TA937), 2) Alternative HSUVs (CKD stages 1-2: VALIANT; CKD stages 3-5: Cooper et al. (2020) with decrement applied for patients with uPCR >1g/g based on VALIANT data analysis), and 3) eGFR decline for those in stable disease (-0.18 mL/min/1.73 m² decline per 3-month cycle (Guppy et al. 2024)).

EAG comment: The main concerns of the EAG relate to: a) parameters included in the deterministic one-way sensitivity analysis, b) resetting of cell values in the economic model when running company scenario analyses or the probabilistic sensitivity analysis, and c) variation in probabilistic results.

- a) The CS deterministic one-way sensitivity analysis excluded various parameters, including baseline/post-transplant distributions of CKD stage and uPCR, uPCR transitions (for intervention/comparators), and probability of CKD 5 patients starting dialysis, uPCR distributions after relapse (before and after transplant). CQ B29 requested justification for their exclusion and an updated economic model with deterministic one-way sensitivity analysis results including these parameters. In response, the company included the probability of CKD 5 patients starting dialysis. However, the company suggest that, given that varying baseline distributions, uPCR transitions, and uPCR distributions would also impact other parameters (to still sum to 100%), it would no longer be a one-way sensitivity analysis. The EAG believes that such parameters should still be included in the deterministic one-way sensitivity analysis with transparency regarding which other parameters would also be impacted, to support with interpretability.
- b) When conducting its analyses, the EAG noted that when running the probabilistic sensitivity analysis or when running company scenario analyses within the “Scenarios” tab, cells used to implement EAG analyses (predominantly if-statements) were overwritten with hard coded values. As such, a disclaimer has been included in the “EAG” sheet stating the EAG model should not be saved after running such analyses, or a copy should be created first. The company should resolve this issue in an updated economic model for future analyses.
- c) Slight variation exists when running probabilistic analyses in the economic model. Further, the EAG noted that five simulations were not recorded in the “PSA simulations” sheet of the company’s post-clarification economic model (rows 578-582). The EAG wishes to see a fixed seed for reproducibility of probabilistic results and for the company to correct the issue with some iterations not being recorded when running the PSA.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

As per CS Section 3.11.1, the economic model was developed based on clinical insights from an advisory board meeting with nephrologists in April 2024, and through follow-up interviews conducted in May 2025. The advisory board validated modelling assumptions pertaining to: generalisability of results from VALIANT to the economic model population, relationship between uPCR levels and eGFR, HSUVs, uPCR health state cut-offs, model cost drivers and considerations, transplant assumptions, and treatment discontinuation/stopping rules. The follow-up interviews focussed on the relationship between uPCR and eGFR, HSUVs, eGFR decline assumptions, spontaneous remission, transplant assumptions, treatment discontinuation/stopping rules, treatment restart criteria, costing and resource use, and C3G and primary IC-MPGN modelling comparability.

5.3.2 Technical verification

The CS stated that model programming validation was conducted by a secondary health economist to ensure the accuracy of all input parameters and the correctness of the calculations used within the model. No details were provided regarding the conducted tests, nor the results/outcomes of such tests.

5.3.3 *Comparisons with other technology appraisals*

Cross-validation with other technology appraisals was not explicitly mentioned in the CS Section 3.11.3. The CS states that external validation against other published economic evaluations was not considered feasible, provided that no existing cost effectiveness models were identified for any treatment within IC-MPGN or C3G.

5.3.4 *Comparison with external data used to develop the economic model*

Validation of external data used to develop the economic model was not explicitly mentioned in the CS Section 3.11.3. The CS states that external validation against other published economic evaluations was not considered feasible, provided that no existing cost effectiveness models were identified for any treatment within IC-MPGN or C3G.

5.3.5 *Comparison with external data not used to develop the economic model*

Cross-validation with external data not used to develop the economic model was not explicitly mentioned in the CS Section 3.11.3. The CS states that external validation against other published economic evaluations was not considered feasible, provided that no existing cost effectiveness models were identified for any treatment within IC-MPGN or C3G.

EAG comment: The main concerns of the EAG relate to: a) lack of transparency regarding technical verification of the model, b) limited of cross-validation with other relevant technology appraisals, and c) lack of external validation of the economic model and modelled outcomes.

- a) CS Section 3.12 suggested that model programming validation was conducted by a secondary health economist to ensure accuracy and correctness of the calculations within the economic model. The EAG requested detail regarding the tests and associated outcomes of the validation, as well as a completed TECH-VER checklist. The company did not provide these, owing to limited time. The EAG emphasises the request to validate the economic model.
- b) No cross-validation was provided in the CS with other relevant technology appraisals. The EAG requested (CQ B31) cross-validation regarding the model structure, modelling assumptions, model inputs (including clinical effectiveness [i.e., time to CKD stage, eGFR slopes, and uPCR], health state utility values, and resource use and costs), intermediate outcomes, and final outcomes compared with the following previous technology appraisals, in addition to any other relevant TAs identified: TA942, TA937, TA890, TA882, TA877, TA825, TA809, TA807, TA775, TA623, TA599, TA481, TA358. In response, the company suggest that only previous appraisals relating to IgA nephropathy are considered relevant. Table 90 of the clarification response provides a comparison with previous appraisals for IgA nephropathy and C3G (TA937, TA1074, and GID-TA11331). Further, model inputs were not compared/extracted from the included TAs – only the time horizon, cycle length, model structure, health states, intermediate/final outcomes, treatment waning assumption, and sources of inputs were extracted. However, further comparison was also provided in clarification response Table 91 with GID-TA11331 (Committee Papers for iptacopan). Comparisons were made to key discounted model outcomes. Costs for SoC in the present submission are largely consistent with SoC in the iptacopan CS but are significantly higher than in the EAGs base-case for TA11331. The QALY for SoC are largely lower in the present submission. One offered potential explanation is the higher number of transplants predicted over the course of a patient's lifetime, however the EAG in TA11331 suggested that the number of transplants may be underestimated here. No explanation was provided for the difference in SoC costs highlighted. The EAG

emphasises that it would like to see a cross-validation expanded to include all aspects requested in the clarification letter (i.e., addition of any other modelling assumptions and model inputs - including clinical effectiveness [i.e., time to CKD stage, eGFR slopes, and uPCR], health state utility values, and resource use and costs) and for all the listed TAs.

- c) The EAG requested further external validation of the economic model. That is, the EAG requested that the company report on the validity of the model structure, modelling assumptions, model inputs, intermediate outcomes, as well as final outcomes (including what was assessed, what the considerations were, and conclusions). In response, the company suggest that, given the rare nature of diseases and lack of published models, external validation was conducted through expert elicitation. Whilst the EAG accepts the lack of published economic models in the present disease areas, a full comparison to evidence (not) used to develop the economic model remains lacking.

6. External Assessment Group's additional analyses

Iptacopan + SoC is currently not considered a relevant comparator and was therefore not included in the additional analyses conducted by the EAG.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:⁵²

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016):

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

No fixing errors.

6.1.1.2 Fixing violations

1. Exclusion of cost savings and QALY gains associated with kidney reallocation (Section 4.2.5).
Excluding cost savings and QALY gains associated with reallocation of kidneys to patients outside the C3G/IC-MPGN population.

6.1.1.3 Matters of judgement

2. Exclusion of treatment effect in the estimation of eGFR decline (Section 4.2.6).
Excluding the treatment covariate from the linear regression model used to estimate eGFR decline.
3. Exclusion of a stable disease health state (Section 4.2.6).
Excluding the stable disease health state by setting the transition probabilities to this health state to zero.
4. Exclusion of the impact of CV events (Sections 4.2.6 and 4.2.7).
Excluding the increased risk of CV events and impact on HRQoL and costs.
5. Alternative utility values for CKD stage 3-5 and dialysis health states (Section 4.2.8).
Informing CKD stage 3-5 and dialysis health state utility values based on GID-TA11331.
6. Exclusion of additional utility decrement (Section 4.2.8).
Excluding the additional utility decrement for health states with uPCR levels >1 g/g.
7. Inclusion of vaccination and antibiotics costs (Section 4.2.9).
Included the costs associated with vaccines and antibiotics for patients on pegcetacoplan.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

8. Alternative definition and duration of stable disease (Section 4.2.6).
Defining stable disease as uPCR <1.0 g/g for a duration of 12 months.
9. Alternative definition and duration of stable disease without discontinuation of treatment (Section 4.2.6)
Defining stable disease as uPCR <1.0 g/g for a duration of 12 months and assuming that patients remain on treatment.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Inclusion of a stable disease health state	4.2.2 / 4.2.6	Bias and indirectness	Scenario analyses related to the definition and duration of stable disease, the probability of disease stabilisation, eGFR decline and treatment discontinuation during stable disease, as well as assuming no stable disease occurring in either treatment strategy.	+ / -	Partly	Empirical evidence to support the necessity and validity of including a stable disease health state.
Inclusion of costs and benefits outside of the NHS and Personal Social Services (PSS)	4.2.5	Methods	Analyses excluding cost savings and QALY gains associated with the reallocation of kidneys no longer required by patients treated with	+	Yes	N/A

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
			pegcetacoplan or iptacopan. Presenting any benefits and cost-savings from kidney reallocation in a disaggregated format, separately from the reference-case results.			
Use of unequal follow-up durations (52 weeks vs 26 weeks) in treatment effect estimation	4.2.6	Bias and indirectness	To align the comparison, both arms should be modelled using data from the same follow-up duration (i.e., baseline to 26 weeks), corresponding to the randomised controlled period of the VALIANT trial.	+	No	Re-estimation of treatment effects using 26-week data for both arms for all treatment effect parameters used in the health economic model. Adding scenario analyses testing the impact of using 52-week versus 26-week data.
Use of two separate regression models with limited data and validity	4.2.6	Methods / imprecision	A single, integrated	+	No	Re-estimation using all

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
			regression framework jointly modelling uPCR and eGFR (or a sequential model with uPCR as a predictor of eGFR) using all available repeated measures. Diagnostics such as residual plots, goodness-of-fit statistics and scenario analyses should be presented to assess model robustness. Adopt a simpler modelling approach such as in GID-TA11331; iptacopan for treating complement 3			longitudinal trial data (e.g., mixed-effects models). Full presentation of regression diagnostics and sensitivity analyses. Exploration of model structures consistent with prior NICE appraisals in C3G.

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
			glomerulopathy, requiring more straight forward statistical models.			
Identical transition probabilities before and after transplant	4.2.6	Bias and indirectness	Differentiating post-transplant transition probabilities and outcomes from pre-transplant ones, informed by registry data, published studies, or clinical expert elicitation. A simpler approach, for the post-transplant phase, as used in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy) would have	+	No	Use of registry or real-world data on post-transplant outcomes in C3G. Using a simpler approach for the post-transplant phase, as used in GID-TA11331 (iptacopan for treating complement 3 glomerulopathy), potentially in combination with external post-transplant data. Sensitivity analysis varying post-transplant transition

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
			been preferred and might have allowed the use of external post-transplant data.			probabilities and mortality risks. Validation of post-transplant assumptions by clinical experts.
Issues related to the VALIANT health-related quality of life data and methods to inform CKD stage 1 and 2 utility values.	4.2.8	Methods / bias and indirectness	The EAG has suggested to align the HRQoL regression model structure with the CS health economic model (2) using more refined regression approaches (3), an in-depth assessment of missing data and adequate imputation techniques (3), as well as to use the standard errors from regressions (4).	+ / -	No	During clarification stage, the EAG requested to the company should align the regression model with the CS health economic model, provide further assessment of missing data in VALIANT and exploration of imputation, and consecutively use mixed effects regression models for repeated measures.

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Validity of the chosen CKD stage 3-5, and dialysis utility values.	4.2.8	Bias and indirectness	The EAG requested cross-validation with utility values from the literature and requested scenario analyses exploring these. Due to limited evidence in the CS population, the EAG used utilities from GID-TA11331 (i.e., APPEAR C3G, Jesky et al. 2016, Lee et al. (2005)) adjusted in that submission for the C3G population in its base-case.	+	No	Analyses of additional (patient-level) EQ-5D data on CKD stage 3+ C3G/IC-MPGN patients, age- and gender adjustments for the CS patient population might help to resolve this key issue.
Exclusion of pegcetacoplan administration costs	4.2.9	Bias and indirectness	Evidence regarding the distribution of patients that would be	+	No	Further supporting evidence as to the proportion of patients on

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
			administered i) by a healthcare professional and ii) by the patients or caregiver. Scenario analysis incorporating administration costs for patients whose treatment was administered by a healthcare professional and the cost associated with providing instructions to patients that are self-administered (including the cost of the syringe system).			pegcetacoplan that would be self-administered and receive doses in the hospital. A scenario analysis assessing the impact of assuming that all patients would receive all doses by a healthcare professional in a hospital.
Limited validation of the economic model	5.3	Transparency / unavailability	Internal validation: The EAG requested detail regarding	+ / -	No	The validation exercises as requested by the EAG in its

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
			the tests and associated outcomes of the validation, as well as a completed TECH-VER checklist. Cross-validation: The EAG requested cross-validation to various TAs. External validation: The EAG requested external validation with reference to evidence (not) used to develop the economic model.			clarification letter.
^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; ^b Explored C3G = complement 3 glomerulopathy; C3GN = C3 glomerulonephritis; CKD = chronic kidney disease; CS = company submission; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; ICER = incremental cost effectiveness ratio; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal and Social Services; QALY = quality-adjusted life year; TA = technology appraisal; uPCR = urinary protein to creatinine ratio						

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6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the “EAG” sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic/probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (WTP: £20,000)	iNHB (WTP: £30,000)
Deterministic							
CS deterministic base-case							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£35,798	██████	██████
Fixing violations (1-Exclusion of kidney transplant opportunity costs and benefits)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£165,388	██████	██████
Matter of Judgement (2- Exclusion of treatment effect in eGFR)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£68,468	██████	██████
Matter of Judgement (3- Exclusion of stable disease health state)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£272,573	██████	██████

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (WTP: £20,000)	iNHB (WTP: £30,000)
Matter of Judgement (4- Exclusion of cardiovascular events [risk, disutility, cost])							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£34,951	██████	██████
Matter of Judgement (5- Remove utility decrement for health states with uPCR levels >1 g/g for CKD 3-5)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£37,115	██████	██████
Matter of Judgement (6- Inform utility values for CKD stages 3-5 and HD and PD in line with iptacoplan appraisal [i.e., 3-4 based on APPEAR C3G, 5 based on Jesky, and HD/PD based on Lee])							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£41,127	██████	██████
Matter of Judgement (7- Include vaccine and antibiotic costs for pegcetacoplan)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£35,941	██████	██████
EAG deterministic base-case							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£2,507,775	██████	██████
Probabilistic							
CS probabilistic base-case							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (WTP: £20,000)	iNHB (WTP: £30,000)
SoC	██████	██████	██████	██████	£36,954	██████	██████
EAG probabilistic base-case							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£2,501,697	██████	██████
CKD = chronic kidney disease; CS = company submission; EAG = external assessment group; g/g = grams of protein per gram of creatinine; eGFR = estimated glomerular filtration rate; HD = haemodialysis; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; PD = peritoneal dialysis; QALY = quality-adjusted life year; SoC = standard of care; uPCR = urinary protein to creatinine ratio; WTP = willingness-to-pay							

Table 6.3: Deterministic/probabilistic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (WTP: £20,000)	iNHB (WTP: £30,000)
Deterministic							
EAG deterministic base-case							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£2,507,775	██████	██████
Scenario Analysis (8-Add stable disease, with 1.0 g/g definition and 12-month duration)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£794,837	██████	██████
Scenario Analysis (9-Add stable disease, with 1.0 g/g definition, 12-month duration, and no treatment discontinuation)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£4,553,413	██████	██████

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (WTP: £20,000)	iNHB (WTP: £30,000)
Probabilistic							
EAG probabilistic base-case							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£2,501,697	██████	██████
Scenario Analysis (8-Add stable disease, with 1.0 g/g definition and 12-month duration)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£765,797	██████	██████
Scenario Analysis (9-Add stable disease, with 1.0 g/g definition, 12-month duration, and no treatment discontinuation)							
Pegcetacoplan +SoC	██████	██████	█	█	-	█	█
SoC	██████	██████	██████	██████	£4,185,560	██████	██████
EAG = External Assessment Group; g/g = grams of protein per gram of creatinine; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life year; SoC = standard of care; WTP = willingness-to-pay							

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was £2,501,697 per QALY gained. [REDACTED]

[REDACTED]. The most influential adjustments were exclusion of the stable disease health state and kidney transplant opportunity costs and benefits. The ICER increased most in the scenario analysis with alternative assumptions regarding the stable disease health state.

6.4 Conclusions of the cost effectiveness section

The CS, Appendices E, F and G and response to clarification^{1, 3, 10-12} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use in the treatment of patients with C3G or primary IC-MPGN. Searches were conducted in September 2024 and updated in May 2025. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases, HTA agency websites, grey literature resources and conference proceedings were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The company's cost effectiveness model partly complied with the NICE reference case. Deviations from the NICE reference case related to the inclusion of cost savings and QALY gains of reallocated kidneys outside the scope of the NICE reference case, and use of the US tariff in the study informing CKD 3-5 health state utility values. The most prominent issues highlighted by the EAG are reported in the key issue Tables in Section 1.5.

Firstly, the inclusion of a stable disease health state lacks empirical justification and appears structurally redundant, introducing unnecessary complexity. In addition, the model incorporates cost savings and health benefits on patients outside the C3G/IC-MPGN population, which fall outside the scope of the NICE reference case. Both the 'stable disease' health state and cost savings and health benefits on patients outside the C3G/IC-MPGN population were excluded from the EAG base-case. Treatment effectiveness was asymmetrically derived using 26-week data for the SoC arm and 52-week data for pegcetacoplan + SoC, based on the EAG's understanding of the economic model, potentially overestimating the pegcetacoplan treatment effect. Furthermore, regression models for uPCR and eGFR were based on limited data, had limited credibility and (face) validity and may double-count treatment effects. To avoid double-counting of treatment effects, the EAG therefore excluded the treatment covariate from the regression model estimating eGFR decline in its base-case. Furthermore, transition probabilities were assumed identical pre- and post-transplant, which lacks clinical plausibility and may underestimate post-transplant risks. These issues collectively compromise the credibility of (long-term) outcomes. The EAG recommends re-estimation of treatment effects using consistent 26-week data, use of longitudinal modelling techniques (e.g., mixed-effects models), and incorporation of real-world or registry data for post-transplant transitions. This potentially combined with the use of a simpler model structure (e.g., without uPCR based health states and a simpler post-transplant approach, i.e., similar to GID-TA11331), supported by expert validation and sensitivity analyses. Next to that, estimation of regression models for utility values for CKD stages 1–2 from pooled VALIANT data was based on few observation points, potentially not reflecting the course of the disease. The EAG noted that these regression models were misaligned with the model structure which differentiates by additional uPCR levels and treats CKD stages separately, and questioned the methodology used to estimate utility values. For CKD stages 3–5 and dialysis, literature-based values were derived from studies with limited

relevance to the CS population, small sample sizes, and using the US tariff for HRQoL valuation. The EAG therefore informed these utility values in line with GID-TA11331. Further, the assumption that all patients self-administer pegcetacoplan lacks validation, which may underestimate administration costs. Finally, validation of the economic model was insufficient, with missing documentation on programming checks, TECH-VER, cross-validation with prior appraisals, and external validation.

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was £2,501,697 per QALY gained. [REDACTED]

[REDACTED]. The most influential adjustments were exclusion of the stable disease health state and kidney transplant opportunity costs and benefits. The ICER increased most in the scenario analysis with alternative assumptions regarding the stable disease health state.

In summary, there is large remaining uncertainty about the effectiveness and cost effectiveness of pegcetacoplan + SoC. Compared with other recent NICE appraisals in C3G (i.e., GID-TA11331; iptacopan for treating complement 3 glomerulopathy), 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 TAs, 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.

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8. Appendix – clinical expert questions and answers

Population

1. Generalisability of VALIANT patients baseline characteristics to UK clinical practice.
 - a) The majority of patients in VALIANT are in early CKD stages (i.e., only 3.23% of patients had CKD stage 4 at baseline and no patients had CKD stage 5). Additionally, approximately 77% of patients (96/124) in VALIANT had C3G disease, and 23% of patients IC-MPGN (28/124). Please comment on whether these numbers are generalizable to the UK C3G and IC-MPGN patient populations.

There will be many more patients in the global clinical practice with CKD Stage 4 and 5. However, the absence of these in the VALIANT trial reflects the clinical trial entry criteria of eGFR>30ml/min [cut-off for CKD stage 4]. Patients with lower eGFR were excluded, as were patients with more than moderate chronic damage on biopsy. This reflects a cohort of patients in clinical practice who either presented late – and therefore never could have been treated or those who presented previously but due to lack of treatments have had worsening kidney function over years and now are considered as having too much long-term and irreversible damage. There is no point waiting until function is worse before treating – catch kidney disease early. Patients at stage 4 or 5 CKD can be expected to need renal replacement therapy though it is possible that some patients with stage 4 CKD might be offered treatment and still delay time to kidney failure. These patients that reach kidney failure would potentially benefit for treatment for recurrence of disease.

- b) In terms of C3G vs IC-MPGN numbers, there may be as many IC-MPGN as C3G in UK however they are differentiated on the balance of immuno-staining on biopsy. However, immune-staining techniques vary dramatically across UK which can lead to under- or over-reporting of one compared to the other.
- c) Please comment on the generalisability of the patient baseline characteristics reported in Table 1 below to UK clinical practice.
- d) Age and gender fairly reflects UK RaDaR data of ages of patients that might be expected to have C3G or IC-MPGN. Weight can be assumed to reflect UK age-gender matched distributions. eGFR / CKD stages as above. In terms of urine P:Cr, median P:Cr at presentation would be expected to be in the higher bracket >3g/g but after 6-12 months, P:Cr likely to range from <1g/g to >3g/g. Again, there is bias due to inclusion criteria where urine P:Cr had to be >1g/g. Patients below this are considered to be at lower risk of disease progression though over sufficient years [far beyond the scope that any clinical trial could offer, this threshold would still constitute risk of kidney failure. We do see patients who have ,1g/g urinary protein but we wouldn't treat them as aggressively based upon current practice, reflecting international guidelines which in turn defined trial entry criteria.
- e) The economic model assumes that patients return to the baseline distribution of uPCR levels from VALIANT following a transplant. Please comment on the plausibility of this assumption.
- f) Immediately following transplant, urine P:Cr likely falls to a minimum, before onset of proteinuria due to disease recurrence. Over time, there would be a distribution of urine P:Cr which could reflect current prevalent cases. So the assumption is plausible for prevalent patients.

Table 1: Patient baseline characteristics applied in the company's economic model.

Parameter		Value	Use in the model
Age (mean)		25.97 years	Mortality risk, general population age/sex disutility
Weight (mean)		63.09 kg	SoC basket costs
Percentage male		43.55%	Mortality risk, general population age/sex disutility
Baseline distribution of CKD stages	CKD 1	45.97%	Starting health state distributions
	CKD 2	20.97%	
	CKD 3	29.84%	
	CKD 4	3.23%	
	CKD 5	0.00%	
Baseline distribution of uPCR levels	<1g/g	8.87%	
	1-3 g/g	58.87%	
	>3g/g	32.26%	

Model Structure

2. Clinical plausibility of health state transitions, and cycle length justification.
 - a) The company defined health states based on uPCR levels and CKD stage (through eGFR decline). uPCR levels were subdivided into uPCR < 1.5 g/g, uPCR 1.5-2.0 g/g, uPCR 2.0-3.0 g/g, and uPCR > 3.0 g/g, whereas eGFR decline for CKD staging was subdivided into eGFR > 90 mL/min/1.73 m² (CKD 1), 90-60 mL/min/1.73 m² (CKD 2), 59-30 mL/min/1.73 m² (CKD 3), 29-15 mL/min/1.73 m² (CKD 4) and <15 mL/min/1.73 m² (CKD 5). Please comment on the clinical plausibility of the different uPCR and eGFR cut-offs.
 - b) CKD cut-offs are reasonable and reflect clinical practice as clinically meaningful cut-offs across which there may be greater risk of complications associated with CKD, especially going from CKD 3 to 4, and 4 to 5. Increasing urine P:Cr associates with increasing risk of progression of CKD. Capturing urine P:Cr down to 0.5g/g or 1g/g would have been preferable where progression is far less likely. Patients with urine P:Cr >3g/g are likely nephrotic and have additional symptom burden as a result.
 - c) In the CS it is stated that “Technically, transitions between any combination of CKD and uPCR health states are allowed”. Please comment on the clinical plausibility of this statement. More specifically, would backward transitions (e.g., from CKD 3 to CKD 2) or bigger jumps (e.g., from CKD 2 to CKD 4 or from uPCR >3.0 to uPCR <1.5 within one model cycle of 3 months) be considered clinically plausible?

- d) Urine P:Cr can improve very quickly and certainly within a 3 month cycle. Similarly a relapse could cause urine P:Cr to go from nothing to $>>3\text{g/g}$ overnight. Worsening kidney function over time due to C3G / IC-MPGN can be quick but probably no more than 1 CKD stage would be unusual except in very acute inflammatory and/or crescentic disease which would have been excluded from trials. Moving down or up a CKD stage may simply reflect a change in eGFR at the border between one stage or the other due to variability in serum creatinine measurements. However, sustained decreases in eGFR over several cycles amounting to years is expected in uncontrolled C3G / IC-MPGN. Adequate treatment would be expected to blunt this decline and progression through CKD stages. In some scenarios, eGFR may even rise, therefore going to a milder CKD stage.
- e) The economic model employs a 3-month cycle length to capture cost and QALY impacts. From your clinical perspective, is a 3-month cycle sufficiently granular compared to shorter cycle lengths (e.g., 1 month/4 weeks as used in other TAs) for capturing the progression of CKD in this patient population? Please explain your reasoning.

I would accept 3-month cycle length for capturing CKD progression in the vast majority of patients with C3G / IC-MPGN. Whilst there is a high risk of progression to kidney failure in this patient group, the eGFR decline should not lead to worsening CKD stage from month to month. Such acute decline can occur but is not the dominant phenotype.

3. Assumptions related to dialysis (initiation) and transplantation

- a) What is your clinical perspective on initiating dialysis and kidney transplant after staying in the CKD stage 5 health state (i.e., $\text{eGFR} < 15 \text{ mL/min/1.73m}^2$) for one model cycle?
- b) Patients invariably do not initiate dialysis or have transplants within months of reaching $\text{eGFR} < 15 \text{ mL/min}$. 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 quoted in 3b. Considering NG107 from 3c, the difference between a starting eGFR of 8 mL/min to 6 mL/min may reflect one or two cycles at most. This also describes a scenario where patients have very low eGFR but remain asymptomatic. The thresholds set in 3b are very reasonable. It could take several cycles to go from eGFR 15 to actually starting dialysis. Similarly, whilst patients may be eligible for transplant at $\text{eGFR} < 15 \text{ mL/min}$, it would be unusual for such a patient to be offered a transplant quickly. If deceased donor, these patients usually have not started dialysis yet and whilst pre-emptive transplant in this group is an aspiration, a patient newly with $\text{eGFR} < 15$ would be far less likely to be called for transplant, and certainly not within 3 months. Similarly, if being worked up for a live donor transplant, it would be unusual to transplant so promptly after eGFR has reached 15 mL/min.
- c) How do you view this threshold in comparison to previous NICE appraisals (e.g., GID-TA11331 and TA358, where initiation was set at < 7.6 and $< 8.5 \text{ mL/min/1.73 m}^2$ respectively)?
- d) In light of NICE guideline NG107, which recommends starting replacement therapy “around 5 to 7 mL/min/1.73 m^2 ,” how clinically plausible is the submission’s threshold? Would thresholds at 5, 7, or a midpoint (6 mL/min/1.73 m^2) be more representative of current clinical practice?
- e) The model assumes that 100% of patients transition to dialysis, i.e., assuming no pre-emptive transplants. Please comment on the clinical plausibility of this assumption.

- f) Renal registry data would report pre-pandemic levels of pre-emptive transplants as high as 8-9%, slightly lower since pandemic, down to 6.6% in 2022. So a majority of patients to commence dialysis, though 100% is rather pessimistic.
- g) The model assumes that 88% of patients undergo haemodialysis and 12% undergo peritoneal dialysis. Please comment on the clinical plausibility of this assumption.
- h) In the same 2022 report, that 6.6% had a pre-emptive transplant, 74.7% had HD and 18.8% had PD. Of all dialysis patients, this is roughly 80% HD vs 20% PD. The figures in the model overstate HD slightly but there will be regional variation.
- i) The model assumes that 16.8% of patients are unsuitable for transplantation, regardless of the number of prior transplantations. Please comment on the clinical plausibility of the estimate and the assumption that this estimate does not depend on the number of prior transplantations.
- j) The figure of 16.8% seems high. In c3g and IC-MPGN, patients are often younger and without fewer co-morbidities so fewer would be considered not transplantable. Having previous transplants can make it more difficult to get a good match or there may be additional challenges. Having previous transplants may have an impact though in practice, most transplants will be a first transplant, with second, third or even fourth transplants being generally less common. However, in C3G and IC-MPGN were recurrence rates have been historically high, it is plausible for patients to have multiple failed transplants. Graft failure can lead to pre-emptive future transplants also – we are looking at smaller numbers. There is no theoretical maximum number of transplants but in my practice, I am aware of a handful of patients who have had 3 transplants but more would be very rare. It would be reasonable to cap at 4 transplants perhaps and certainly would only predict a minority would reach this number. This helps with 3g.
- k) The model assumes that patients can receive multiple transplants, with graft failure leading back to dialysis. In your view, is this assumption consistent with clinical practice? Would it be more appropriate to cap the maximum number of graft failures and subsequent transplants?
- l) Do you think the model should differentiate between early versus late graft failure in terms of transition probabilities? What are the clinical implications of such distinctions?
- m) Ultimately any graft failure leads to either dialysis or re-transplantation. Early graft failure could be primary non-function leading to re-listing and potentially very early offer of re-transplantation. Early graft failure due to aggressive recurrence disease is unusual but would be perceived as a relative contraindication to another transplant.

Intervention and comparators

- 4. Based on Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines, SoC in the CS includes ACEi/ARB (■■■■%), immunosuppressants (■■■■%), systemic corticosteroids (■■■■%), and SGLT2i (■■■■%).
 - a) Please comment on whether the KDIGO clinical guidelines are in accordance with UK clinical practice.
 - b) UK clinicians generally follow KDIGO in C3G / IC-MPGN. It should be remembered that standard of care is an accepted practice based on experience, not evidence. Where there is sufficient proteinuria, inflammation and/or falling kidney function,

clinicians will want to offer a treatment that may include immunosuppression even if the evidence base is poor.

- c) Clinically, should these proportions be assumed fixed over time, or is there evidence that patients switch between treatments as their disease progresses?
- d) Some clinicians escalate from MMF as initial immunosuppression to other forms including cyclophosphamide, rituximab and plasma exchange in response to failure to control therapy. This escalation is due to lack of effective therapies. Equally, patients may escalate from ACEi only to addition of MMF / steroids. Over time, patients either improve and stop immunosuppression or lose kidney function or get side effects and equally stop immunosuppression. There isn't any prospective data however to show that improvements in kidney disease are due to immunosuppression.
- e) In clinical practice, are patients typically managed with monotherapy, or can they receive multiple SoC treatments simultaneously?
- f) Patients often receive multiple SOC treatments. It is recognised that patients with kidney disease should have maximal reduction in proteinuria to protect renal prognosis for the maximal length of time. This is especially true of younger patients who might be able to have 10-20 years of kidney function but still need dialysis when they are 40 years old.
- g) If patients do receive multiple SoC treatments concurrently, how should the combined treatment effect be accounted for in an economic model? Should the joint effect be considered additive or is there a more nuanced interaction?
- h) There are no trials to show how different SOC treatments interact. However, registry data shows progression of kidney failure repeatedly despite any combination of SOC treatments.
- i) Should eculizumab be incorporated as a comparator (consistent with the final scope), specifically for patients with a history of kidney transplant and highly aggressive recurrent disease, in the economic model? What are the key clinical considerations for its inclusion?
- j) Eculizumab has been used in only 10 patients since 2017 [as part of the clinical commissioning policy 16054/P] with C3G – the eligibility criteria are cited within the document. It delays graft loss but not prevent it. It could be considered a comparator but the use case should be very carefully considered as it is a treatment that is used in a small minority of transplant patients with C3G. treatment using pegcetacoplan in a majority of patients with recurrent C3G and some proteinuria would likely prevent the need for most, if not all [10 in 8 years] cases of eculizumab.

Treatment effectiveness

- 5. The company assumes a constant pegcetacoplan treatment effect, as well as additional benefits of pegcetacoplan related to cardiovascular events and CKD mortality.
 - a) Please elaborate on the clinical plausibility of assuming of assuming no treatment waning, i.e., that there is a constant lifetime pegcetacoplan treatment effect compared to SoC.
 - b) Depends what we mean by treatment waning. The effect of pegcetacoplan on the complement system is likely to be constant. Any residual CKD and proteinuria will lead to progressive CKD despite ongoing use of pegcetacoplan. Whist there are

worsening clinical parameters, these should not be considered an effect of treatment waning.

- c) Please elaborate on inclusion of additional benefits of pegcetacoplan versus SoC related to cardiovascular events

CKD and subsequent kidney failure associates with cardiovascular risk and mortality. Pegcetacoplan might benefit patients by delaying or preventing progression of CKD rather than any direct effect of pegcetacoplan on cardiovascular risk of mortality associated with CKD.

- d) Please elaborate on inclusion of additional benefits of pegcetacoplan versus SoC related to CKD mortality

- 6. The company included a stable disease health state, defined as uPCR less than 0.5 g/g. For patients in the stable disease health state, it was assumed to not experience eGFR decline or transition to later CKD stages.

- a) Please elaborate on the existence of a “stable disease” phase (where patients “maintained stable eGFR”) in C3G.

If there is minimal disease activity, arguably at the lowest or absent urine P:Cr, the likelihood of progressive CKD falls dramatically. urine P:Cr of less than 0.5g/g is a reasonable threshold to ascribe this stable disease phase to. There already are some patients who seem to have disease remission with little or no proteinuria [P:Cr <0.5g/g or even lower] who have little or no ongoing injury to kidney so nephron loss if any is not obviously detectable by serum creatinine measurements, and therefore do not have any apparent decline in eGFR and not observed to progress to more severe CKD stages. Long term follow up and demonstration that eGFR decline is not obvious over many years is required to prove this.

- b) Please comment on the plausibility that for a proportion of patients their disease can stabilise and that no eGFR decline nor transitions to more severe CKD stages is assumed.
 - c) Please comment on, if applicable, whether stable disease should be defined by uPCR (or different outcome(s)) and whether the cut-off of 0.5 g/g is plausible.

Defining such a state by urine P:Cr seems reasonable for most patients though there are always exceptions. I would accept that urine P:Cr <0.5g/g offers the prospect of longer-term stable disease but lower urine P:Cr would be even better.

- d) CS Section 3.2.2 suggests that, to assess disease stabilisation, a biopsy may be required. Please comment on whether you agree on this statement, what specific biopsy would be required and whether this applies to assessment of disease stabilisation for all patients regardless of treatment received.

A kidney biopsy would be a good way to understand disease activity but in practice, tends to be used when improvement appears modest at best and by inference, the repeat kidney biopsy is expected to show ongoing active disease and that the current treatment is not wholly effective. It is plausible that repeat kidney biopsy helps demonstrate excellent histological response but clinicians will use all of the information available and as a kidney biopsy is an invasive procedure isn't a test that is frequently used currently to look for evidence of disease stabilisation. There are no longitudinal studies that confirm remission in patients with C3G. Previous retrospective reports describe clinical remission. The best longitudinal data is in recent trials and most notable in the follow up biopsies in the NOBLE and VALIANT studies.

- 7. In the company's economic model, it was assumed that [REDACTED] % of patients discontinued pegcetacoplan treatment every three months. Patients who progress to CKD stage 5 or require dialysis are also assumed to discontinue treatment, and patients who achieve stable disease

discontinue all treatment. For patients on treatment, a constant pegcetacoplan treatment effect was assumed, i.e. no waning of the pegcetacoplan treatment effect.

- a) Please comment on the plausibility of the [REDACTED] % discontinuation rate every three months for patients on pegcetacoplan. How does this compare to other treatments in chronic kidney disease?
 - b) The [REDACTED] figure was based on the clinical trial data. It is likely that patients with C3G / IC-MPGN are highly motivated as they potentially have a lot to benefit from an effective treatment. Stopping due to side effects as measured in the current duration of the clinical trials at a rate of [REDACTED] seems reasonable in the foreseeable future but the practice in the clinic may differ.
 - c) Please comment on the plausibility of the assumption that patients who achieve stable disease temporarily discontinue their treatment and continue again when relapsing.
 - d) It is reasonable to expect that patients discontinue and restart if disease manifestations worsen.
 - e) Please comment on the plausibility of assuming a constant iptacopan treatment effect for as long as patients remain on treatment.
 - f) In the same way that pegcetacoplan's effect on the alternative pathway isn't likely to wane, I would expect the same of iptacopan.
8. The company assumes identical transition probabilities, i.e. rate of disease progression, pre- and post-transplant.
- a) Please elaborate on the clinical plausibility of assuming equal transition probabilities, i.e. rate of disease progression, pre- and post-transplant. Could you provide any supporting literature?

Post-transplant recurrence is predictable and can be pre-empted by surveillance following transplant. What is less clear is the optimal timing for intervention.

<https://pubmed.ncbi.nlm.nih.gov/39116277/> this is high rate of histological recurrence vs high rates of graft loss. <https://link.springer.com/article/10.1007/s00467-024-06476-5> significantly lower graft outcomes compared to controls due to C3G recurrence. Post-transplant recurrence of C3G or IC-mPGN should be considered at least as likely to result in graft loss as pre-transplant disease and progression to kidney failure.

Adverse Events

9. The company stated that no adverse events were considered in the economic modelling as few patients in each VALIANT treatment arm experienced serious treatment-emergent adverse events during its randomised controlled period. However, disutilities and costs were assigned to adverse reactions due to cardiovascular events.
 - a) Please comment on whether the adverse events reported in CS Table 49 (Section 2.11) from the randomised controlled period of VALIANT are reflective of UK clinical practice.
 - b) AE are specified in more detail in Table 50. These reflects typical AE in clinical practice and appear balanced between treatment and placebo group. Treatment emergent AE are affect a minority of patients and again are balanced between the two groups.
 - c) Please comment on whether you expect differences in AE/safety profiles between pegcetacoplan, iptacopan and SoC.

- d) Pegcetacoplan is given s/c so there may be more local skin reactions. Both pegcetacoplan and iptacoplan have risk of infection due encapsulated organisms that is managed by vaccination and consideration of antibiotics. Conventional immunosuppression such as MMF / prednisolone have well documented side effects also which seem to be different to those experienced by patients in trials of pegcetacoplan or iptacoplan.
- e) Please comment on whether, based on your experience, particularly cardiovascular events should be incorporated or not (despite the findings and thresholds applied on the clinical trial data, as well as the company's statement that the impact of adverse events would be implicitly captured in VALIANT).
- f) Not sure what is asked here... happy to discuss.
- g) In the APL2-C3G-310 Final Clinical Study Report, Section 9.7.2.1., the company stated that "If a PT [Preferred Term] was reported more than once for the same participant, that participant would only be counted once in the incidence for that PT." Please comment on this rationale.
- h) I can't find section 9.7.2.1 – I wonder if this reflects multiple infusion site related Aes? Or persistent symptoms such as GI disorders. I would like to see that these multiple counts for different patients were balanced across the two groups and that none were related to SAEs.

Health-related quality of life

10. For CKD stage 1 and 2, health-related quality of life (HRQoL) was informed by EQ-5D-5L data from the VALIANT study.

- a) The company decided to pool HRQoL for stages 1 and 2. Do you agree with the company's approach, taking both into account disease presentation and development as well as the amount of measurements available at the different stages? Please explain your answer.
- b) CKD Stages 1 and 2 are very mild and not normally referred to renal services in UK in isolation. Pooling these two groups with this in mind seems reasonable. More important would be the impact of disease activity due to complement activation in C3G and also proteinuria.
- c) Please discuss the representativeness of the utility values to inform HRQoL derived from the VALIANT study for the primary C3G as well as primary IC-MPGN patient population differentiating between adolescents aged 12-17 years and adults, for UK clinical practice.
- d) which data are we looking at here? Happy to discuss.
- e) Please discuss whether the observation timepoints (i.e., baseline, week 26, week 52) available in VALIANT are sufficient to capture the impact of the course of the disease on HRQoL, in terms of frequency and duration between measurements.

HRQoL may change dramatically due to reversal of nephrotic syndrome and improvement in proteinuria over weeks and months and certainly in the time-frame of the trial. It is less likely that patients' CKD status and/or symptoms relating to CKD changes significantly over the same period aside from any that might reach kidney failure.

11. Health state utility values for CKD stages 3 to 5, as well as for dialysis (haemodialysis (HD), peritoneal dialysis (PD)) and undergoing transplant were informed by literature.
 - a) The literature study populations diverge from the CS population. Please comment on whether there is reason to question the validity and applicability of the estimates from these studies to inform HRQoL for the CS population, for instance in terms of comorbidities? Please comment on the representativeness of the chosen utility values for UK clinical practice.
 - b) Utility values will have to be extrapolated as these patients with CKD stage 5 on HD / PD were not included in the trial. However, these are health states that are entirely predictable as outcomes of SOC - notably when we state that C3G and IC-MPGN are causes of progressive CKD. It is reasonable to expect that these are the lowest health states as determined by utility value.
 - c) Please comment on the company's assumption for the kidney transplant utility value, setting it effectively equal to HD.
 - d) the company state in section 3.4.4 that the category undergoing transplant – with lowest utility covers the period of time around the kidney transplant surgery, a major operation. This seems reasonable. To be clear, following transplant and if / when successful patients become independent of dialysis and as stated by company, these patients then revert to a health state comparable to non-transplant patients depending on CKD stage and urine PCR.

Costs and Resource Use

12. The company stated that pegcetacoplan can be administered by a healthcare professional or administered by the patient or caregiver following proper instructions with a commercially available syringe system infusion pump. In your experience, what proportion of patients in UK clinical practice are expected to receive pegcetacoplan self-administered, and what proportion by a healthcare professional?

In the clinical trials that I was involved in, patients had in-centre drug administration. I am aware that self-administration was an option but I don't have data or experience on the relative proportions.

13. Please clarify whether patients treated with pegcetacoplan or iptacoplan would receive (prophylactic) antibiotics (specify) during treatment, and if so, which ones and at which frequency?

Vaccinations against meningococci, pneumococci and Hib were mandatory in trials. At the NRCTC, we recommend antibiotics in patients receiving eculizumab for aHUS on the basis that not all serotypes are covered by vaccines. Preventative antibiotics are not mandated on product label as far as I am aware but they seem a proportionate precaution, especially if there is additional immunosuppression such as in transplant patients. Guidance is along the lines of post-splenectomy patients with pen V twice daily whilst on treatment being something to consider. Erythromycin and guidance from local microbiology based on local sensitivities would be next line.

14. Based on Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines, SoC in the CS includes ACEi/ARB (), immunosuppressants (), systemic corticosteroids (), and SGLT2i (). The exact treatment regimens are modelled as components of the SoC basket, along with the proportion of patients receiving each component.

- a) Please comment on the reflectiveness of the treatment classes in the SoC basket of UK clinical practice.
- b) Has this been answered in Q4?
- c) Please comment on the reflectiveness of the proportions of patients within each treatment class of UK clinical practice.
- d) Has this been answered in Q4?
- e) Please comment on the plausibility of assuming that the proportion of patients receiving each treatment class of the SoC basket is the same regardless of whether SoC is given in combination with pegcetacoplan, iptacopan or alone.
- f) I would expect ACEi/Arb to be given at a similar proportion, largely reflecting product licenses that were based on clinical trial entry criteria. If either pegcetacoplan or iptacopan are available, and if permitted, clinicians may be more likely to opt for these before trying other SOC treatments on the basis that they have been robustly evaluated in prospective RCTs. I would expect international guidelines to reflect this and to push clinicians to treatments that have been adopted into clinical practice but not based on robust studies.

Single Technology Appraisal

Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over [ID6489]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 20 November 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Issue 1 Inaccurate suggestion that CKD 5 patients would be treated with pegcetacoplan

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 13 of its report in table 1.2, the EAG states: In reference to patient in CKD 4 and CKD 5 <i>“However, the company responded in such a way that suggested they wished to retain them as long as they were not on dialysis or post-transplant.”</i>	Provide clarification that patients in CKD 5 are not expected to continue to receive pegcetacoplan.	The company’s economic model restricted pegcetacoplan use to only those patients in CKD 1-4. As such, the company do not anticipate patients in CKD 5 would continue to receive pegcetacoplan, instead these patients would be prepared to initiate renal replacement therapy.	Amended.

Issue 2 Inaccurate reporting of pegcetacoplan treatment positioning

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 14 of its report in table 1.3, the EAG states: <i>“They also stated that eculizumab had been excluded as a comparator in the iptacopan appraisal, which the EAG confirmed</i>	Clarification of the EAG’s opinion on the positioning of pegcetacoplan should be stated more clearly and should take into consideration the identical positioning of pegcetacoplan and iptacopan (despite the terminated appraisal).	The current wording suggests that the anticipated positioning for pegcetacoplan differs from the previously discussed positioning for iptacopan, which is not the case. Given that a comparison against eculizumab was not deemed	Not a factual inaccuracy – the sentence makes no comparison between iptacopan and pegcetacoplan positioning.

<i>had been reported in the draft guidance. However, the EAG understood that this was on the basis of iptacopan being prescribed earlier than eculizumab post-transplant, which is not currently standard of care.”</i>		appropriate based on clinical input during the terminated appraisal of iptacopan, and the fact that the positioning of pegcetacoplan is identical to that discussed in the iptacopan appraisal committee meeting, this comparison would not be justified.	

Issue 3 Misinterpretation of data for changes from baseline in eGFR

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 15 – “However, it appears that there is a gradual reduction in the improvement in outcomes for those randomised to pegcetacoplan in VALIANT after the end of the randomised controlled period of 26 weeks. This includes eGFR, where the change from baseline is –1.49 (–5.89, 2.89) at 26 weeks, and –3.65 (–8.93 to 1.62) at 52 weeks. This is despite the company	Clarification to be added regarding the fact that no significant differences in outcomes were reported and all patients beyond 26 weeks received pegcetacoplan, which would lead to treatment related improved outcomes in the “placebo” arm between weeks 26 and 52.	The current wording suggests a difference in outcomes that is not fully supported by the data. In the pegcetacoplan-to-pegcetacoplan group, pegcetacoplan stabilised eGFR through 52 weeks. After initially declining in the placebo-to-pegcetacoplan group, pegcetacoplan similarly stabilised eGFR for the remainder of the treatment period. After 52 weeks, the LS	Not a factual inaccuracy – these statements refer to the fact that the design precluded a comparison between pegcetacoplan and placebo (no pegcetacoplan) beyond 26 weeks, but it can be observed that eGFR continues to decrease on pegcetacoplan between 26 and 52 weeks, which does not seem consistent with

claiming that: "... eGFR remained stable in the pegcetacoplan-to-pegcetacoplan group through 52 weeks." It would therefore appear that the treatment effect (i.e., difference in outcomes between pegcetacoplan and placebo) might also diminish if patients in the placebo arm had continued on placebo instead of switching to pegcetacoplan" Page 76 – "Also, there does appear to be a deterioration in other outcomes for those randomised to pegcetacoplan between 26 and 52 weeks, including for eGFR." Page 102 – "However, it appears that there was a gradual decrease in the improvement in outcomes for those randomised to pegcetacoplan after the end of the randomised controlled period of 26 weeks in		mean CFB in eGFR was comparable for both groups, although slightly more negative in the placebo-to-pegcetacoplan group. However, the magnitude is small and the CIs for the treatment groups overlapped (pegcetacoplan-to-pegcetacoplan) indicating that the difference between the treatment groups was not meaningful. The conclusion drawn by the EAG appears to be a misinterpretation of the clinical trial design in VALIANT. Page 15 states "<i>It would therefore appear that the treatment effect (i.e., difference in outcomes between pegcetacoplan and placebo) might also diminish if patients in the placebo arm had continued on placebo instead of switching to pegcetacoplan.</i>". Patients in the placebo arm switched to	the claim of stabilisation, and might suggest a reduction in the treatment effect i.e. the difference between pegcetacoplan and placebo. However, the EAG has amended the wording in order to avoid the misunderstanding that such a decrease has been observed.

VALIANT. This includes eGFR, which showed that the change from baseline was –1.49 (95% CI –5.89 to 2.89) at 26 weeks, and –3.65 (95% CI –8.93 to 1.62) at 52 weeks.”		pegcetacoplan after 26 weeks, and likely would have seen a continuing worsening of outcomes such as eGFR if they had stayed on placebo (consistent with the decline seen in the first 26 weeks of the trial). Similarly, the same misinterpretation is present on page 76 of the EAG report.	

Issue 4 Contradictory conclusion

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 20 of its report (and in subsequent related sections), the EAG states: <i>“The company included cost savings and QALY gains associated with the reallocation of kidneys no longer required by patients treated with pegcetacoplan or iptacopan to other NHS patients.</i> <i>These cost savings and health benefits accruing to patients outside the C3G/IC-MPGN</i>	Remove the key issue or reword description to avoid contradictory statements relating to the economic model capturing NHS savings/QALY gains, with a conclusion that these are not part of the NHS and PSS perspective.	The description is contradictory as the first sentence indicates the costs and benefits capture those incurred by other NHS patients, but the conclusion is that these fall outside of the NHS and PSS perspective. Technologies that deliver benefits beyond the NHS and PSS (for example, treatments that reduce drug	Not a factual inaccuracy. The NICE reference case focuses on costs and outcomes relevant to the NHS and PSS, but primarily in relation to the population under appraisal.

<i>population represent indirect effects which are not directly attributable to the intervention's impact on the treated population (or their carers) and hence fall outside the scope of the NICE reference case, which specifies a perspective limited to the NHS and PSS."</i> In Sobi's view, this statement is contradictory, stating cost savings/QALY gains are captured for other NHS patients, but simultaneously not considered part of the NHS and PSS perspective.		misuse may also lower crime rates) are classified as non-reference case in the NICE Manual. However, because the cost-effectiveness analysis includes only costs and benefits accruing to the NHS, the EAG's conclusion is not considered accurate.	

Issue 5 Request for clarification of data already provided in the company submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment

On page 15 of its report, the EAG states that “Further evidence on the treatment effect beyond 26 weeks would seem to be unavailable. Nevertheless, clarification could be provided on: - the long-term follow up of patients in VALIANT - how patients were recruited to VALE, and why some from the placebo arm of VALIANT were recruited.” Sobi notes that both bullet points in this statement are addressed in the company evidence submission.	This suggestion should be removed, as clarification has previously been provided.	The current statement does not reflect the evidence provided in section 2 of the company submission. In section 2.3.1.1 of the company submission, it is stated that patients in the placebo arm of the VALIANT trial during the randomised controlled period (RCP) subsequently received pegcetacoplan in the open-label period (OLP) of the trial for those 26 weeks, thereby explaining the recruitment of placebo arm patients to VALE, where patients experienced clinical benefit from that treatment, in the opinion of the investigator . Patients in the follow-up period of the VALIANT study did not receive treatment with pegcetacoplan as this was a wash out period (as shown in Figure 5 of the company submission), and therefore cannot provide any additional evidence beyond the initial 52 weeks of the trial for which data was provided in section 2.6.1.5 of the company submission (RCP and OLP periods). Specifically, more information on this is provided on page 50 of the	Not a factual inaccuracy. However, the text has been amended to acknowledge that no data with follow-up beyond 26 weeks are available for patients who did not switch to pegcetacoplan.

Furthermore, inclusion of placebo patients in open-label extension trials is common practice and it is unclear why this requires explanation.		company submission: “At the end of the RCP, participants from both groups proceeded to the 26-week OLP, in which all participants were treated with pegcetacoplan twice weekly...An estimated 100 participants (of the 120 enrolled in VALIANT), who in the opinion of the investigator had experienced clinical benefit from pegcetacoplan, were invited to participate in the long-term extension study (APL2-C3G-314/VALE).”	

Issue 6 Key Issue 9 does not acknowledge analysis provided in the original company submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Table 1.10 on pages 18 and 19 of its report, the EAG makes the following suggestion: <i>“To align the comparison, both arms should be modelled using data from the same follow-up duration</i>	Removal of Key Issue 9 Removal of Key Issue 3 from Table 6.1	Both requests from the EAG were provided as Scenario 1 in the original company submission: 1. Re-estimation of treatment effects using 26-week data for both arms for all treatment effect parameters used	Not a factual inaccuracy. This scenario analysis, nor transparency regarding its implementation was provided in the company’s updated economic model in response to clarification.

<i>(i.e., baseline to 26 weeks), corresponding to the randomised controlled period of the VALIANT trial.”</i> However, Sobi notes that these analyses have already been provided in Scenario 1 of the original company submission on (Company evidence submission, page 197, Table 101, Scenario 1).		in the health economic model. 2. Adding scenario analyses testing the impact of using 52-week versus 26-week data for treatment effect estimation. Accordingly, this issue has already been addressed in the original company submission and should not be reflected in the EAG report.	

Issue 7 References to modelling structures from a terminated appraisal

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 19 of its report, the EAG suggests an alternative approach: <i>“As well as adopting a simpler modelling approach, i.e. model structure, such as in GID-TA11331; iptacopan for treating C3G, requiring</i>	Remove reference to model structure suggestions used in previous terminated appraisals.	There are no currently approved products in primary C3G or IC-MPGN, and Sobi considers it unhelpful and inappropriate to reference methods from a product for which the appraisal was terminated.	Not a factual inaccuracy.

<i>more straight forward statistical models”</i> The EAG then suggests the following additional analyses: <i>“Exploration of model structures consistent with prior NICE appraisals in C3G.”</i> On pages 22 and 23 of its report the EAG goes on to state: <i>“Compared with other recent NICE appraisals in complement 3 glomerulopathy (C3G) (i.e., GID-TA11331; iptacopan for treating complement 3 glomerulopathy), the company’s submission introduces a level of structural and analytical complexity that is not justified by the available evidence.”</i> And on page 141: <i>“Using a simpler approach for the post-transplant phase, as used in GID-TA11331</i>		As highlighted in clarification responses B4e-f, prior model structures for CKD were considered (as used in GID-TA11331), but were considered to fail to capture the important nephrotic component of C3G and IC-MPGN.	

<i>(iptacopan for treating complement 3 glomerulopathy), potentially in combination with external post-transplant data.”</i>			

Issue 8 Misleading wording around clarification requests (Key issue 12)

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On pages 20 and 21 of its report, the EAG states: <i>“During clarification stage, the EAG requested the company to align the HRQoL regression model with the CS health economic model structure, provide further assessment of missing data in VALIANT and exploration of imputation, and consecutively use mixed effects regression models to appropriately incorporate longitudinal data.”</i>	A summary of the response to these requests should be included in the summary to accurately reflect the appraisal process to date.	The current wording does not reflect additional information provided by the Company as part of the clarification response provided on 16 th October 2025.	Not a factual inaccuracy.

Sobi provided responses to this clarification request (Sobi response to clarification question B21, submitted on 16th October 2025.) The EAG report fails to reflect the company response, which is unhelpful and misleading. The wording does not consider the responses provided to clarification question B21, which were submitted on 16th October 2025.			

Issue 9 Misleading wording around clarification requests (Key issue 13)

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 21 of its report, the EAG states: <i>“Analyses of additional (patient-level) EQ-5D data on CKD stage 3+ C3G/IC-MPGN patients, as well as age- and gender adjustments of literature-</i>	Keep request for “Analyses of additional (patient-level) EQ-5D data on CKD stage 3+ C3G/IC-MPGN patients”. Remove request for “age- and gender adjustments of literature-based utility values for the CS patient population”.	Age-adjusted utilities were provided in Scenario 5 of the original company submission (gender adjustments were not possible due to lack of reported gender split in the literature), and further clarified in response to clarification question B22b. Additionally, age-sex adjusted	Not a factual inaccuracy.

<i>based utility values for the CS patient population might help to resolve this key issue.”</i> Sobi addressed elements of this key issue in its original evidence submission (scenario 5) and in its clarification response (Sobi responses to clarification questions B22a and B22b, submitted on 16th October 2025.) The EAG report fails to reflect the company response, which is unhelpful and misleading.		values from GID-TA11331 were also provided as scenario in response to clarification question B22a)v). If the intention of the wording in the report was for further analysis to be conducted, in addition to the above, then the report should provide further clarity on the exact requested analysis.	

Issue 10 Factual inaccuracies regarding the SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 34 of its report, the EAG states: <i>“The company do not confirm how data extraction was conducted, and as such the EAG must consider that</i>	The first statement should be removed. The second statement should be amended to reflect the provision of this data in the company submission, i.e., “Screening was conducted with	Appendix B of the CS includes the following description: <i>“Two reviewers worked independently to screen records and extract data, with any disagreements or</i>	Amended.

<i>the there is an increased likelihood of error and bias. Had the data extraction been conducted as the screening had with duplicate extractions and disagreements resolved by discussion then this would constitute a reliable and robust method reasonable to minimise errors and biases.”</i> <i>“Screening was conducted with appropriate methods for reducing error and bias but it was not reported how data extraction was conducted. While it might be assumed that a similar method was employed as was used in screening, it is imperative that the company clearly reports and describes such methods. For this reason, the EAG has concerns about errors and biases that may be present.”</i> <i>“As with data extraction, the company have not provided</i>	appropriate methods for reducing error and bias”. The third statement should be removed.	<i>discrepancies resolved through discussion and agreement between the reviewers. Studies were selected for inclusion via a 2-stage screening process. At the first-pass stage, all abstracts and titles identified by the searches were screened according to the predefined selection (PICOS) criteria. All records selected at first-pass were then screened at second-pass (full-text stage) by the same 2 reviewers. The full texts of studies meeting inclusion criteria at this stage were included in the review and progressed to data extraction, critical appraisal and ITC feasibility assessment.”</i> As highlighted in bold text, it was indicated that two reviewers worked to screen and extract data, therefore the statements made by the EAG are not factually accurate and should be updated.	

<i>any information on how many reviewers were involved, whether there were duplicate appraisals conducted independently, or if not, whether appraisals were checked by a second reviewer for accuracy and consistency.”</i>			

Issue 11 Incorrect labelling – Figure 3.4 and Table 3.11

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 47 of its report, the EAG contains the following caption: “Figure 3.4: NOBLE Study design (Part A)” This figure relates to the DISCOVERY study. There is no Part A in this trial. (Note, the caption in table 3.11 on page 47 contains a typo)	The text should be amended as follows: “Figure 3.4: DISCOVERY Study design” “Table 3.11: DISCOVERY eligibility criteria”	The current labelling relates to an incorrect study for pegcetacoplan.	Amended

Issue 12 Misleading wording regarding VALIANT trial design

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 76 of its report, the EAG states: <i>“In the longer term, the magnitude of the primary outcome on pegcetacoplan seems to be maintained in the OLP i.e., after the RCP of 26 weeks. However, the magnitude of the outcome of those randomised to placebo also improved.”</i>	The comment should be clarified to indicate that all patients in the OLP received pegcetacoplan.	After 26 weeks all participants received pegcetacoplan - e.g. the proportion of participants who achieved the composite renal endpoint at week 52 was 38.1% in the pegcetacoplan-to-pegcetacoplan group and 36.1% in the placebo-to-pegcetacoplan group.	The EAG have amended the text to avoid the misleading impression that the data on those randomised to placebo can be used to infer anything about the treatment effect post-26 weeks.

Issue 13 Misreported trials in section 3 of the EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The reporting of the pegcetacoplan trials is	Adjustment of the report structure to capture the evidence submitted by the	As stated in section 2.2 of the company submission regarding NOBLE and DISCOVERY trials, “Neither	Not a factual inaccuracy. However, the EAG have added some text to provide justification for

inconsistent within the EAG report. Section 3.2.2 includes 4 trials identified by the company submission (VALIANT, VALE, NOBLE and DISCOVERY), whilst 3.2.3 and 3.2.4 only report information on VALIANT and NOBLE, and 3.2.5-3.2.7 focus on VALIANT and VALE. This is inconsistent with the company submission, which focused on VALIANT and VALE as the main sources of evidence for pegcetacoplan. NOBLE and DISCOVERY were reported in appendix J and included only as supportive clinical information.	company, with justification if information is not included.	study was used to populate the economic model because they had low sample sizes and differed appropriately from the pivotal VALIANT trials, limiting the appropriateness of pooling outcomes for implementation into the model. However, the results of both studies support the clinical impact of pegcetacoplan on proteinuria reduction and stabilisation of the decline in eGFR, both of which are key drivers of the economic model. Therefore, details of these phase II studies have been included in Appendix J: Supporting clinical effectiveness evidence from phase II trials. Evidence for NOBLE is taken from Bomback et. al. 2025 (89) (week 12 data) and the clinical study report (week 52 data) (102), whilst evidence for DISCOVERY is taken from Dixon 2023 (79)." The current structure of the EAG report does not include	the exclusion of DISCOVERY and NOBLE from further analysis.

		the limited details of statistical analysis of VALE, which provides longer term evidence for the use of pegcetacoplan. It also provides information on NOBLE, but not DISCOVERY, with no clear justification given.	

Issue 14 Incorrect reporting of uPCR level assumptions post-transplant

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 109 of its report, the EAG states: <i>“Patients are assumed to return to the baseline distribution of uPCR levels sourced from VALIANT following a transplant.”</i>	At the time of transplant, all patients have a UPCR <1.0 g/g. In the subsequent cycle, ■■■ of patients are assumed to be in the UPCR <1.0 g/g sub-group, and ■■■ in the UPCR 1.0-3.0 g/g health state.	This assumption was updated following additional clinical feedback received during clarification questions (B3).	Amended to reflect that following all patients post-transplant initially have a uPCR <1.0 g/g and that the expected rate of increase in proteinuria as observed in the VALIANT placebo arm is applied in subsequent model cycles.

Issue 15 Incorrect model schematic

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 110 of its report, the EAG includes a figure reported as: “Figure 4.1: Model structure”	Include updated model schematic provided in response to clarification question B4a:	The current model schematic in the EAG report is based on an old iteration that was updated at the clarification stage.	Amended as proposed.

Issue 16 Matter of judgement used without substantive supporting evidence

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 114 of its report the EAG states: <i>“The EAG noted that the NICE reference case focuses on costs and outcomes relevant to the NHS and PSS, but primarily in relation to the population under appraisal.”</i>	Remove “but primarily in relation to the population under appraisal” or provide substantive evidence from the NICE guidance to support this statement. Alternatively, highlight that this statement is based on the EAG’s judgement if supporting evidence is not identified.	The conclusion that these analyses are primarily related to the population under appraisal is not considered by the company to be explicit in the NICE guidance. Therefore, such statements of judgement from the EAG should be substantiated with evidence from the NICE guidance or supporting documents or highlighted as EAG judgement.	Not a factual inaccuracy.

Issue 17 Inaccurate conclusion of prior TA committee discussions

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 114 and 115 of its report, the EAG states: <i>“Although the manual allows for consideration of health</i>	As with Issue 16, substantive evidence should be provided to support this statement: “Although the manual allows for consideration of health	See justification for Issue 16 The discussion between the EAG/committee in TA809 considered the transplantation	Not a factual inaccuracy. “Someone else” in this context is interpreted by the EAG as someone

<i>effects on carers and other individuals, this is typically limited to those directly affected by the condition or its treatment (as seems to be the case in TA809, in which the intervention facilitates access to transplantation for the treated population)."</i>	effects on carers and other individuals, this is typically limited to those directly affected by the condition or its treatment". Remove "(as seems to be the case in TA809, in which the intervention facilitates access to transplantation for the treated population)"	of scarce kidneys beyond the treated population (i.e. "The committee understood that any donor kidney used with imlifidase could have been used for someone else who is likely to incur lower costs, and have better outcomes and equal related savings from avoiding dialysis"). As such, the EAGs conclusion does not appear to accurately represent the conclusion of the committee in TA809.	else with the same condition under appraisal.

Issue 18 Clarification that eGFR improvements are possible in the short-termN

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 115 and 116 of its report, the EAG states: <i>"For patients with uPCR <1.0 g/g on pegcetacoplan + SoC, the model predicted an increase in eGFR. As this was considered clinically</i>	P115-116: "As this was considered clinically implausible in the long-term, the company assumed no change in eGFR in this subgroup" P118: "Also, the regression model predicted an increase in eGFR (for patients with uPCR <1.0 g/g on	Clinical feedback suggests that short-term increases in eGFR—particularly in the context of acute kidney injury—are possible, whereas sustained long-term	Not a factual inaccuracy. This is a summary of the CS e.g. related to the statement "Patients with uPCR < 1.0 treated with pegcetacoplan showed an increase in eGFR, indicating stabilisation of

<i>implausible, the company assumed no change in eGFR in this subgroup (CS Table 71)."</i> And on page 118: <i>"Also, the regression model predicted an increase in eGFR (for patients with uPCR <1.0 g/g on pegcetacoplan + SoC), which was considered clinically implausible (and hence set no change in eGFR in this subgroup), which illustrates the limited clinical validity of this regression model"</i>	pegcetacoplan + SoC), which was considered clinically implausible in the long-term (and hence set no change in eGFR in this subgroup), which illustrates the limited clinical validity of this regression model"	improvements are generally considered unlikely. Additional wording is suggested to acknowledge this feedback from clinicians.	kidney function. However, extrapolating this eGFR improvement over the model time horizon was considered inappropriate and lacking clinical face validity. Therefore, a conservative assumption was made: no change in eGFR was applied for patients with uPCR < 1.0 while on pegcetacoplan treatment".

Issue 19 Request for clarification of data already provided in the company submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 117 of its report the EAG explores impact of CKD on mortality (section 4.2.6.4.2):	Remove discussion around discrepancy in time-points. Alternatively, include acknowledgement that these analyses were provided in	As these analyses were provided at the time of the original company submission, the request for	Not a factual inaccuracy.

<i>“a) 26-week placebo data and 52-week pegcetacoplan data from VALIANT were used in the model base-case”</i> <i>“Hence, the EAG would have preferred to use baseline and 26 weeks data for both pegcetacoplan + SoC and SoC.”</i>	the original company submission (Scenario 1).	these scenarios in the EAG report appears redundant.	

Issue 20 Request for data provided at clarification stage – regression models

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 118 the EAG states: <i>“Unfortunately, the company did not respond to clarification question B11 regarding justification for this approach nor were the requested scenario analyses (using one regression model) provided.”</i>	Remove statement.	This statement is factually incorrect and misleading. A response to this clarification question was provided on 16 th October 2025.	Not a factual inaccuracy. Clarification question B11a does not justify why the current approach is more appropriate than a single regression model (i.e. two linked regressions were used rather than a parsimonious single model). Also given the risk of double counting

			(which B11b does not address)

Issue 21 Request for clarification provided at the clarification stage – CV event justification

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 119 the EAG states: <i>“Justification and supporting evidence were requested by the EAG for including CV events in the CS base-case (Clarification question B17). Unfortunately, no detailed responses were provided by the company”</i>	Include acknowledgement that responses to clarification B19a provide supporting literature for the relationship between CKD progression and CV events.	Although limited responses to B17 were provided due to time constraints, B19a does provide justifications for the inclusion of CV events distinct from AEs.	Not a factual inaccuracy. No detailed responses were provided for the assumption that deviation from normal eGFR (~90 mL/min/1.73m ²) increased the risk of CV events, nor were the identified sources justified.

Issue 22 Unclear on the mismatch outlined between utility analysis and the economic model structure

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 123 the EAG states:	Provide further clarification as to the mismatch the EAG is referring to.	Following clarification of the model schematic (B4a) the	Not a factual inaccuracy.

<i>“This results in a mismatch with the health economic model structure with regard to uPCR thresholds as well as CKD stage differentiation”</i> And on page 142: <i>“During clarification stage, the EAG requested to the company should align the regression model with the CS health economic model, provide further assessment of missing data in VALIANT and exploration of imputation, and consecutively use mixed effects regression models for repeated measures.”</i>		utility analysis is considered to align with the model structure.	

Issue 23 Additional scenarios provided at clarification not reported to support EAG expectation

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 125, the EAG states: <i>“As this health state applies only for one model cycle, the impact on cost effectiveness is expected to be minor”</i>	Add supporting reference to scenarios provided by the company in response to clarification question B22d)iii).	The scenario provided as part of the clarification responses helps to support the EAGs expectation that the impact of this parameter on the model results is minor.	Not a factual inaccuracy.

Issue 24 Incorrect reporting of iNHB in Table 5.1.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 131 the EAG states: <i>Table 5.1</i> Iptacopan +SoC iNHB results	Provide corrected actual iNHB values from the economic model.	Results show “Dominant” which is not a relevant outcome for iNHB. As such, these should be reported as the iNHB as shown in the economic model.	Amended as proposed.

Issue 25 Inclusion of fixing of errors identified in the PSA to explain changes to PSA results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 132 the EAG states: <i>“b) In response to the clarification letter, the company updated its base-case (Table 5.2) including the following changes”</i>	Include wording outlining the correction of error identified in the PSA as a result of EAG clarification question B29b.	The most significant change in the PSA results was due to corrections to errors identified following EAG clarification (B29b). As such, this should be highlighted as a reason for the change in PSA results between original CS and post-clarification	Amended as proposed.

Issue 26 Redundant sentence referring to “fixing error”

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 136 the EAG states: <i>“The ‘fixing error’ adjustments were combined and the other EAG analyses were performed also incorporating these ‘fixing error’ adjustments given the EAG considered that the</i>	This statement should be deleted, or acknowledgement made to clarify no “fixing errors” were identified.	Since no fixing errors were identified, this statement may be misleading for readers of the report.	Not a factual inaccuracy. In section 6.1.1.1 it was made clear that there were no errors identified that required fixing.

<i>'fixing error' adjustments corrected unequivocally wrong issues"</i>			

Issue 27 Categorisation of savings and QALY gains associated with kidney reallocation

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 137, the EAG states: <i>"1. Exclusion of cost savings and QALY gains associated with kidney reallocation (Section 4.2.5). Excluding cost savings and QALY gains associated with reallocation of kidneys to patients outside the C3G/IC-MPGN population"</i>	The company propose that this Key Issue is categorised under "Matters of judgement".	Please see justification for Issue 4. Without the suggested additional evidence from the NICE guidance to support the EAGs concerns with the inclusion of savings/QALY gains from reallocation of kidneys in the company base case, it is considered this is a matter of judgement and interpretation of the current NICE guidance. Therefore, the key issue should be categorised as such within the EAG report.	Not a factual inaccuracy. The EAG considers this issue a violation of the reference case.

Issue 28 Unclear labelling of Key issue 2 in Table 6.1

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 137, the EAG states: <i>“Inclusion of costs and benefits outside of the NHS and Personal Social Services (PSS)”</i>	Removal of key issue. Alternatively, update wording to more accurately reflect concern “Inclusion of costs and benefits outside of NICE reference case”.	Please see justification for Issue 4. Without the suggested additional evidence from the NICE guidance to support the EAGs concerns with the inclusion of savings/QALY gains from reallocation of kidneys in the company base case, it is considered this is a matter of judgement and interpretation of the current NICE guidance. Therefore, the key issue should be categorised as such within the EAG report.	Not a factual inaccuracy.

Issue 29 Conclusion fails to acknowledge additional analysis provided

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 150, the EAG states: <i>“Treatment effectiveness was asymmetrically derived using 26-week data for the SoC arm and 52-week data for pegcetacoplan + SoC, potentially overestimating the pegcetacoplan treatment effect.”</i>	This statement should acknowledge that scenarios were provided to test this assumption, resulting in lower ICERs for pegcetacoplan when using 26-week data across both model arms. As such, the use of 52-week data in the company base case is not considered to overestimate treatment effect.	Please see justification for Issue 6 concerning provision of 26-week analysis from both trial arms as a scenario in the original company submission (Scenario 1). The results of the scenario indicate that the use of 52-week for pegcetacoplan provided higher ICER results in the economic model compared to the use of 26-week data. Therefore, the treatment effect was not overestimated.	Amended to reflect that the EAGs statement was based on the EAGs understanding of the economic model.

Issue 30 First scenario of Table 6.2 is incorrectly identified as a “Fixing errors”

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 146, the EAG states:	This has been previously referenced in the report as “Fixing violations”.	This has previously been identified as “Fixing	Amended to “fixing violations”.

<i>"Fixing errors (1-Exclusion of kidney transplant opportunity costs and benefits)"</i>	However, please see Issue 27 for full proposed amend.	violations" by the EAG in Section 6.1.1.2 of the report. Please see Issue 27 for full justification for suggested amend to "Matters of judgement".	

Issue 31 Typographical errors

Location of typographical error	Description of suggested correction	EAG comment
Page 109: <i>"HD was assumed to occur three times per week, and PD and daily."</i>	HD was assumed to occur three times per week, and PD once daily.	Amended as proposed.
Page 125: <i>"However, the EAG acknowledges the limitations of this approach, and also conveys to the committee that the majority of the six experts consulted by the company stated that CDK stage 4 and 5 utilities should be lower than 0.74 and 0.73, respectively."</i>	"However, the EAG acknowledges the limitations of this approach, and also conveys to the committee that the majority of the six experts consulted by the company stated that CKD stage 4 and 5 utilities should be lower than 0.74 and 0.73, respectively."	Amended as proposed.

Page 126: <i>“Patient treatment discontinuation for pegcetacoplan or iptacopan due to safety concerns, as per VALIANT estimated as a [REDACTED] per-cycle discontinuation rate, or due to entering CKD stage 5 or dialysis (CS Section 3.6)”</i>	It is believed this should refer to CS Section 3.3.6	Amended as proposed.

Issue 32 Incorrect marking of confidential information

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
Page 112 Section 4.2.2 EAG comment d) <i>“Based on clinical expert feedback, the company in their revised base-case assumes that all patients enter the transplant health state with uPCR</i>	<i>“[REDACTED] of patients remain in the <1.0 g/g subgroup, while [REDACTED] transition to the 1.0–3.0 g/g subgroup”</i> These figures are derived from confidential information from VALIANT and should be marked as such	<i>“[REDACTED] of patients remain in the <1.0 g/g subgroup, while [REDACTED] transition to the 1.0–3.0 g/g subgroup”</i>	Amended

<1.0 g/g, reflecting minimal proteinuria immediately post-transplant. In the subsequent cycle, █ of patients remain in the <1.0 g/g subgroup, while █ transition to the 1.0–3.0 g/g subgroup, based on the uPCR rate increase observed in the placebo arm of the VALIANT trial.”					
Page 122 Table 4.4 Utility value	As requested by NICE following the first company submission, the company has ensured these values are not marked as confidential in the subsequent company submission. As such, these are not				Amended.
		Health state		Utility value	Reference
CKD 1, 2		Remission	0.91	VALIANT	
		uPCR <1 g/g	0.91		
		uPCR 1 g/g-3 g/g	0.84		
		uPCR >3 g/g	0.84		
CKD 3		Remission	0.75	Sidhu et al. 2024	
		uPCR <1 g/g	0.75		

	considered to be confidential	<table> <tr> <td></td><td>uPCR 1 g/g-3 g/g</td><td>0.69</td><td>Sidhu et al. 2024, VALIANT (uPCR disutility applied)</td></tr> <tr> <td></td><td>uPCR >3 g/g</td><td>0.69</td><td></td></tr> <tr> <td rowspan="4">CKD 4, 5</td><td>Remission</td><td>0.58</td><td rowspan="2">Sidhu et al. 2024</td></tr> <tr> <td>uPCR <1 g/g</td><td>0.58</td></tr> <tr> <td>uPCR 1 g/g-3 g/g</td><td>0.52</td><td rowspan="2">Sidhu et al. 2024, VALIANT (uPCR disutility applied)</td></tr> <tr> <td>uPCR >3 g/g</td><td>0.52</td></tr> <tr> <td>HD</td><td>-</td><td>0.44</td><td>Cooper et al. 2020</td></tr> <tr> <td>PD</td><td>-</td><td>0.53</td><td>Cooper et al. 2020</td></tr> <tr> <td>Undergoing transplant</td><td>-</td><td>0.44</td><td>Cooper et al. 2020 (assumption: same as HD utility)</td></tr> <tr> <td colspan="4"> Based on CS Table 85 CKD = chronic kidney disease; CS = company submission; g/g = grams of protein per gram of creatinine; HD = haemodialysis; PD = peritoneal dialysis; uPCR = urinary protein to creatinine ratio </td></tr> </table>		uPCR 1 g/g-3 g/g	0.69	Sidhu et al. 2024, VALIANT (uPCR disutility applied)		uPCR >3 g/g	0.69		CKD 4, 5	Remission	0.58	Sidhu et al. 2024	uPCR <1 g/g	0.58	uPCR 1 g/g-3 g/g	0.52	Sidhu et al. 2024, VALIANT (uPCR disutility applied)	uPCR >3 g/g	0.52	HD	-	0.44	Cooper et al. 2020	PD	-	0.53	Cooper et al. 2020	Undergoing transplant	-	0.44	Cooper et al. 2020 (assumption: same as HD utility)	Based on CS Table 85 CKD = chronic kidney disease; CS = company submission; g/g = grams of protein per gram of creatinine; HD = haemodialysis; PD = peritoneal dialysis; uPCR = urinary protein to creatinine ratio				
	uPCR 1 g/g-3 g/g	0.69	Sidhu et al. 2024, VALIANT (uPCR disutility applied)																																			
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Page 126 <i>“Patient treatment discontinuation for pegcetacoplan or iptacopan due to safety concerns, as per VALIANT estimated as a [REDACTED] per-cycle discontinuation rate, or due to</i>	The discontinuation rate of [REDACTED] was derived from unpublished VALIANT trial data	<i>“Patient treatment discontinuation for pegcetacoplan or iptacopan due to safety concerns, as per VALIANT estimated as a [REDACTED]% per-cycle discontinuation rate, or due to entering CKD stage 5 or dialysis”</i>	Amended.																																			

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Page 132 “a. <i>Assumption that at the time of the transplant, all patients have a uPCR <1.0 g/g. In the subsequent cycle, █████ of patients are assumed to be in the uPCR <1.0 g/g sub-group, and █████ in the uPCR 1.0-3.0 g/g health state.</i>”	Figures █████ and █████ have been derived from unpublished VALIANT trial data	a. <i>Assumption that at the time of the transplant, all patients have a uPCR <1.0 g/g. In the subsequent cycle, █████% of patients are assumed to be in the uPCR <1.0 g/g sub-group, and █████% in the uPCR 1.0-3.0 g/g health state.</i>	Amended.																								
Page 147 Table 6.2 Matter of Judgement (6- Inform utility values for CKD stages 3-5 and HD and PD in line with iptacopan appraisal [i.e., 3-4	iNHB (WTP:£20,000) and iNHB (WTP:£30,000) results have not been highlighted	<table><tr><th colspan="8">Matter of Judgement (6- Inform utility values for CKD stages 3-5 and HD and PD in line with iptacopan appraisal [i.e., 3-4 based on APPEAR C3G, 5 based on Jesky, and HD/PD based on Lee])</th></tr><tr><td>Pegcetacoplan +SoC</td><td>██████</td><td>██████</td><td>██████</td><td>██████</td><td>-</td><td>██████</td><td>██████</td></tr><tr><td>SoC</td><td>██████</td><td>██████</td><td>██████</td><td>██████</td><td>£41,127</td><td>██████</td><td>██████</td></tr></table>	Matter of Judgement (6- Inform utility values for CKD stages 3-5 and HD and PD in line with iptacopan appraisal [i.e., 3-4 based on APPEAR C3G, 5 based on Jesky, and HD/PD based on Lee])								Pegcetacoplan +SoC	██████	██████	██████	██████	-	██████	██████	SoC	██████	██████	██████	██████	£41,127	██████	██████	Amended.
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based on APPEAR
C3G, 5 based on
Jesky, and HD/PD
based on Lee])

Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name:

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

Topic ID:

6489

Managed Access Lead:

Steve Norton

Date of assessment(s):

13/11/2025

Feasibility of successful managed access	Comments / Rationale	
No managed access proposal	Rationale for rating	There is no proposal for managed access. If Committee or other stakeholder wishes for managed access to be considered for this topic, they should contact the Managed Access Team.
	Previous ratings and rationale for change	

Managed Access Proposal	No	
Managed Access Team input at Committee meeting	Requires additional engagement	Consideration of managed access requires discussion with the Managed Access Team

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Unclear	The criteria are partially met. A stronger case is required for whether this treatment is a step-change for patients and clinicians, and for whether relevant data can be collected to resolve uncertainties
Are there outstanding uncertainties that could be resolved with further data collection?	Low	The uncertainties highlighted for this technology would best be resolved by improved analytical approaches. Some would require additional research, probably beyond the scope of managed access. There is no proposal to explain how managed access could be carried out to resolve any of these uncertainties.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Unclear	A range of data sources exist that could be used to provide further evidence, particularly the VALE OLE of the key trial. The UK runs two clinical registries that could also be beneficial. However, the usefulness of all these sources is not clear at this stage with no managed access proposal to describe how data collected would directly resolve identified uncertainties.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	Low	No managed access proposal has been made so this section has not been evaluated in detail
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	Not applicable	As there is no proposal, this has not been investigated in detail

Key questions for committee if Managed Access is considered

1	Will the OLE study (VALE) gather more than the single outcome declared publicly (Proportion of participants with a reduction in urine protein-to-creatinine ratio (uPCR) of at least 50% from the pretreatment value over time)?
2	
3	
4	
5	
6	

Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	
2	
3	
4	
5	
6	