Medicinrådet

Bilag til Medicinrådets vurdering af pegcetacoplan til behandling af C3-glomerulopati eller primær immunkompleks membranoproliferativ glomerulonefritis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. pegcetacoplan
2. Forhandlingsnotat fra Amgros vedr. pegcetacoplan
3. Ansøgers endelige ansøgning vedr. pegcetacoplan

Sobi comments on the preliminary assessment report by DMC

1. **Durability of treatment effect, described as a major uncertainty for this specific assessment.**

In the case of C3G and IC-MPGN, proteinuria and kidney function are not exploratory biomarkers but established prognostic indicators of disease activity and progression, supporting their use as key drivers in extrapolation models. Therefore, the relevant question is not whether extrapolation should be performed, but how it can be performed in the most clinically plausible and evidence-based manner. Excluding or substantially discounting long-term consequences of observed improvements in uPCR and eGFR may risk underestimating the clinical value of treatment. Dialogue with nephrology experts concludes that Aspaveli has the potential to delay or prevent progression to end-stage kidney disease, thereby postponing or avoiding the need for dialysis and kidney transplantation in a proportion of patients. We believe that our modeling approach that is based on longitudinal relationships between changes of eGFR and proteinuria and the subsequent risk of disease progression including kidney failure and its consequences provides a realistic solution for a base case analysis of cost effectiveness of the treatment. To address uncertainties, sensitivity analyses, rather than discounting uncertainties all together, provide valuable information for an informed decision by DMC whether to recommend the drug or not. Registries like the Danish Comp Cure registry will in the future provide more real world evidence about the disease and the treatment to better support future decisions. However, until then there is a very high unmet medical need for these patients that needs to be addressed urgently, where Aspaveli could provide substantial benefits to the patients. To our knowledge [redacted] patients with C3G or IC-MPNG are already being treated in Denmark with Aspaveli.

2. Continued treatment during remission (stable disease)

After dialogue with nephrology experts we conclude that the rationale for including treatment pause during sustained disease control (remission) is based on the expectation that treatment intensity should reflect disease activity and individual patient response, cost of drug and quality of life for the patients. As a conclusion a treatment pause is clinically plausible for a proportion of the patients in remission (stable disease). DMC has made the assumption that none of the patients in remission will receive a treatment pause in the base case which we think represent a conservative and uncertain modelling choice and should be considered as a scenario analysis rather than the base case. We propose to use Sobi's modelled results as the base case because it's motivated by the best available published evidence from patients with other complement mediated kidney diseases and assumptions made by clinical experts that relates to the treatment effects in the pivotal trial.

3. Transplantation-related assumptions

Direct transition from CKD stage 5 to transplantation

We propose implementing the same consideration when modelling also for re-transplantation, to be consistent within the given scenario.

Effects related to reduced demand for donor kidneys

We acknowledge the DMC's intention to focus the primary analysis on treatment-related effects and costs. However, we respectfully believe that the consequences of reduced demand for donor kidneys should be included in the base-case analysis, as they represent a direct consequence of treatment within the healthcare system rather than a broader societal effect.

The DMC's methodological guidance does not explicitly exclude healthcare resource consequences resulting from reduced utilization of donor kidneys. While the guidance states that derived effects not directly related to treatment should not be included, it does not specifically address situations where treatment reduces the consumption of a scarce healthcare resource and thereby affects healthcare utilization and health outcomes within the healthcare sector itself. In our view, donor kidneys differ fundamentally from broader societal consequences such as productivity gains or losses. A donor kidney is a scarce healthcare resource. If treatment delays or even prevents progression to end-stage kidney disease, fewer donor kidneys are required. This directly affects transplantation activity, dialysis utilization, healthcare resource consumption and health outcomes within the publicly funded healthcare system.

Importantly, the relationship between donor kidney utilization and health outcomes is not hypothetical. The health economic model already recognizes that transplant waiting times, access to transplantation, dialysis duration and post-transplant outcomes are associated with both healthcare costs and patient outcomes. Reduced demand for donor kidneys therefore affects the same clinical pathway and healthcare resources that are already considered relevant elsewhere in the model. For this reason, we believe that the consequences of reduced donor kidney utilization should be regarded as treatment-related healthcare effects and therefore included in the base-case analysis. A zero-effect assumption is difficult to reconcile with the Danish healthcare context, where substantial resources are invested in increasing access to kidney transplantation precisely because transplantation is recognised as both clinically superior and more cost-effective than prolonged dialysis. (Cathrine Elgaard Jensen, 2014)

Accordingly, we consider inclusion of donor-kidney-related consequences in the base-case analysis to be the most appropriate approach. Alternative assumptions regarding the magnitude of the effect can then be explored through deterministic sensitivity analyses and scenario analyses.

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LSC/DBS

Forhandlingsnotat

Dato for vurdering i Medicinrådet	02.09.2026
Leverandør	Swedish Orphan Biovitrum AB (Sobi)
Lægemiddel	Aspaveli (pegcetacoplan)
Ansøgt indikation	Behandling af voksne og unge patienter i alderen 12 til 17 år med C3-glomerulopati (C3G) eller primær immunkompleks membranproliferativ glomerulonefritis (IC-MPGN) i kombination med en renin-angiotensin-system (RAS)-hæmmer, medmindre behandling med RAS-hæmmer ikke tolereres eller er kontraindiceret.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Aspaveli:

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP
Aspaveli	1.080 mg (1 stk.)	25.704,75	[redacted]	[redacted]
Aspaveli	1.080 mg (8 stk.)	205.638,00	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale på Aspaveli. Aftalen gælder til den 30.04.2027 med mulighed for at forlænge i 12 måneder.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der findes ikke en godkendt standardbehandling af C3-glomerulopati (C3G), da sygdommen har et meget bredt spektrum af symptomer og klinisk præsentation. Behandling vil derfor være individuelt tilpasset hver patient.

Komplementhæmning med C5-hæmmeren eculizumab, kan forsøges ved hurtigt progredierende sygdom og manglende behandlingsrespons på glukokortikoider og immunsuppression. Eculizumab anvendes dog off-label, og evidensen for at anvende den til C3G og IC-MPGN er mangelfuld, jf. Medicinrådets vurdering af pegcetacoplan til behandling af C3G eller primær immunkompleks membranproliferativ glomerulonefritis.

[redacted]

Aspaveli er anbefalet af Medicinrådet til paroksystisk nokturn hæmoglobinuri (PNH).

Tabel 2 viser de årlige lægemiddeludgifter ved behandling med Aspaveli. For voksne er den anbefalede dosis 1.080 mg 2 gange ugentligt. For unge (12-17 år) er doseringen vægtbaseret, men da Aspaveli kun markedsføres i én styrke, og hætteglasset ikke kan deles, vil lægemiddeludgiften være ens for alle patienter.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Aspaveli	1.080 mg (1 stk.)	1.080 mg 2 gange om ugen på dag 1 og 4, s.c.	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
Sverige	Ikke vurderet	
England	Under vurdering	Link til status

Opsummering

Amgros har en eksisterende aftale på Aspaveli, der gælder til den 30.04.2027 [redacted]

Submission for the Assessment of Aspaveli (pegcetacoplan) for the Treatment of C3 glomerulopathy (C3G) and Immune-complex membranoproliferative glomerulonephritis (IC-MPGN)

Contact Information

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Abbreviations

Acronym	Definition
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
ARB	Angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical

ATMP	Advanced Therapy Medical Products
BSC	Best supportive care
C3	Complement 3
C3G	C3 glomerulopathy
C5	Complement 5
CE	Cost-effective
CEA	Cost-effectiveness analysis
CFB	Change from baseline
CI	Confidence interval
CKD	Chronic kidney disease
CMR	Cochrane Methodology Register
CRG	C3 Glomerulopathy Research Group
CUA	Cost-utility analysis
CV	Cardiovascular
DCD	Donation after circulatory death
DDD	Dense deposit disease
DK	Denmark
DKK	Danish krone
DMC	Danish Medicines Council
DSP	Disease-specific programmes
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMR	Electronic medical records
EQ-5D-3L/5L	EuroQol 5-Dimension, 3/5-Level
ESKD	End-stage kidney disease
EU	European Union

FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FIFO	First in first out
FMU	First-morning urine
HBV	Hepatitis B virus
HCRU	Health care resource utilisation
HCV	Hepatitis C virus
HD	Haemodialysis
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Health state
HSU	Health state utility
HSUV	Health state utility value
HTA	Health Technology Assessment
HUI	Health Utilities Index Mark
IC-MPGN	Immune-complex membranoproliferative glomerulonephritis
ICE	Intercurrent event
ICER	Incremental cost-effectiveness ratio
IF	Immunofluorescence
IQR	Interquartile range
ISN	International Society of Nephrology
ITT	Intention-to-treat
KDQoL	Kidney Disease Quality of Life
LLN	Lower limit of normal
MMF	Mycophenolate Mofetil

MMRM	Mixed Models for Repeated Measures
NA	Not available
NR	Not reported
OLP	Open-label period
OOM	Orders of magnitude
OR	Odds ratio
PD	Pharmacodynamics
PEG	Pegcetacoplan
PGCI	Patient Global Impression of Change
PICOS	Population, intervention, comparator, outcome, study design
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PT	Preferred term
QALY	Quality-adjusted life year
RAAS	Renin-Angiotensin-Aldosterone System
RAS	Renin-Angiotensin System
RCP	Randomised controlled period
RCT	Randomised controlled trial
RDI	Relative dose intensity
RR	Risk ratio
RWE	Real-world evidence
SAE	Serious adverse event
SAS	Statistical analysis system
SC	Subcutaneous

SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SGLT	Sodium-glucose co-transporter
SLR	Systematic literature review
SMC	Scottish Medicines Agency
SOC	System organ class
SoC	Standard of care
TEAE	Treatment-emergent adverse event
UK	United Kingdom
uPCR	Urine protein creatine ratio
USA	United States of America
VAS	Visual analogue scale
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment Questionnaire

1. Information on the Drug

Drug information	
Trade name	Aspaveli
Generic name	Pegcetacoplan
Indication as formulated by the European Medicines Agency (EMA)	Aspaveli is 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) in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated.
Marketing Authorization Holder in Denmark	Swedish Orphan Biovitrum AB (Sobi)
ATC code	L04AJ03
Combination therapy and/or concurrent treatment	Yes, as per indication
Expected date of EU approval (marketing authorisation)	Approved 15 January 2026
Has the drug received a conditional marketing authorisation?	No
Has the drug been in 'accelerated' assessment' at EMA?	No
Does the drug have orphan drug designation?	Yes Pegcetacoplan was first granted orphan designation in the EU for the indication of C3 glomerulopathy on 18 December 2019 (EU/3/19/2201). Pegcetacoplan was granted orphan designation in the EU for the indication of C3 glomerulopathy with or without immune complexes, covering both C3G and primary IC-MPGN on 10 November 2022 (EU/3/22/2716).
Other indications approved by the EMA	Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

Other indications that have been evaluated by the Danish Medicines Council	Yes. The Danish Medicines Council recommends pegcetacoplan for adult patients with the rare blood disease PNH. The recommendation applies to patients who are anaemic (suffer from anaemia) despite at least 3 months of treatment with a C5 inhibitor.
Joint Nordic Assessment (JNHB): **Is current treatment practice comparable across the Nordic countries (DK, FI, IS, NO, SE)?**	Yes
Joint Nordic Assessment (JNHB): **Is the drug suitable for a joint Nordic assessment?**	No, Aspaveli is not a hospital product.
Has a joint European assessment (JCA) been carried out via the EU HTA Regulation?	No
Delivery	BEGR
Packaging – types, sizes/number of units and concentrations	Pack size: 1080 mg, 20 mL single-dose vial, one unit pack and eight unit pack Strength: 54 mg/mL

2. Summary Table

Overview	
Indication relevant to the assessment	Aspaveli is 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) in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated.
Dosage regimen and administration route	Pegcetacoplan is administered 1080 mg twice weekly as a subcutaneous infusion with a commercially available syringe system infusion pump or on-body delivery system, 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.
Comparator selection	No treatment, in addition to standard of care (SoC), including RAS inhibitors, SGLT-2 inhibitors, and immunosuppressive therapy (steroids or mycophenolate mofetil). There are currently no approved therapies for C3G or primary IC-MPGN in Denmark.

Prognosis with current standard treatment (comparator(s))	The prognosis of C3G and primary IC-MPGN is poor, and half of the diagnosed patients steadily progress to kidney failure within ten years, which has significant negative impacts on patient mortality. A greater amount of proteinuria at diagnosis and the persistence of proteinuria have been associated with a higher risk of progression to kidney failure. At kidney failure, patients move on to dialysis and/or kidney transplantation. After kidney transplantation, the underlying disease persists and typically recurs in the transplanted kidney, putting patients at risk of graft failure, dialysis, or the need for repeat transplantation. There is no data on survival rate in a Danish population, but a Finnish study found that 32% of the IC-MPGN patients and 22% of C3G patients on SoC died during the study follow-up of 7.3 (range 0.08-38) years. During the follow-up, 11 (49%) C3G and 16 (43%) IC-MPGN patients developed progressive kidney disease (Kovala et al. 2023).
Type of documentation for the clinical evaluation	Head-to-head study
Main outcomes including at least one outcome for health-related quality of life (difference/improvement compared to comparator(s))	**Reduction in uPCR (proteinuria) at Week 26** compared to baseline - pegcetacoplan vs placebo difference in least square (LS) mean (95% CI): -1.144 (-1.437, -0.851); **Proportion of participants who showed decreases in C3c staining** from baseline - pegcetacoplan vs placebo odds ratio (95% CI): 27.392 (6.477, 115.852); **Adjusted mean difference in mean change of eGFR at Week 26** from baseline - pegcetacoplan vs placebo difference in LS mean (95% CI): 6.312 (0.501, 12.122); **Change from baseline in EQ-5D-5L score at Week 26** – pegcetacoplan vs placebo difference (95% CI): 0.016 (-0.039, 0.071)
Serious adverse events for the intervention and comparator	In the RCP, the most common serious treatment-emergent adverse event (TEAE) was acute kidney injury, which was reported by one participant in the pegcetacoplan group and two participants in the placebo group. No other specific serious TEAE (PT) was experienced by more than one participant. In the OLP, the most common SAEs in the overall study were acute kidney injury (2.5%), dehydration (1.7%) and pyrexia (1.7%). Intervention: Kidney injury 2 (3.3%), pyrexia 0, dehydration 1 (1.6%); Comparator: Kidney injury 1 (1.8%), pyrexia 1 (1.8%), dehydration 1 (1.8%)
Type of health economic analysis	Cost-utility
Health economic model	Markov model
Outcomes and sources for extrapolating patient transitions	Transition probabilities between uPCR health states were derived from a statistical analysis of patient-level data on uPCR from the VALIANT trial. Transition probabilities between

	chronic kidney disease (CKD) states were derived from the eGFR decline estimates by considering the baseline distribution of patients across CKD stages, the eGFR ranges defining each stage, and the corresponding rates of eGFR decline in VALIANT. Stable disease probability was estimated based on the proportion of patients achieving stable disease at end of follow-up in VALIANT. The post-transplant uPCR distribution was derived from VALIANT. For transition probabilities where study data was not viable to use, alternative data sources were used. A summary of the methods and sources used to derive all the transition probabilities in the model is displayed in Table 27.
Instrument and sources for health-related quality of life	EQ-5D-5L (VALIANT), EQ-5D-5L (Cooper et al. 2020), EQ-5D-3L (Hvidberg et al. 2023) (see section 10.3.4 and section 10.4.4)
Life years gained (discounted, corrected for half-cycle and background mortality)	XXXX years
QALYs gained (discounted, corrected for half-cycle and background mortality)	XXXX QALYs
ICER (DKK/QALY) (discounted, corrected for half-cycle and background mortality)	XXXXXXXX
Company's assessment of uncertainty	Pegcetacoplan was found to be XXXXXXXX against SoC only across all deterministic sensitivity analyses

3. Patient Population, Intervention, Choice of Comparator(s) and Outcome(s)

3.1 Patient Population

3.1.1 The Disease

3.1.1.1 Pathophysiology and Differential Classification

C3G and primary IC-MPGN are rare, chronic kidney diseases (CKDs) driven by dysregulation of the complement system, specifically the C3 component. This dysregulation leads to excessive activation and deposition of C3 fragments within the glomeruli (Noris and Remuzzi 2024, Smith et al. 2019). These fragments act as proinflammatory mediators that recruit immune cells and amplify local inflammation resulting in progressive chronic kidney injury (Bomback et al. 2025a, Jayaraman et al. 2024, Wada et al. 2023). In C3G, overactivation of the alternative pathway results in accumulation of C3 fragments and its downstream effectors in the glomerulus, which drives inflammation and progressive kidney damage. This uncontrolled activation is typically caused by genetic abnormalities and/or acquired autoantibodies against complement proteins (Smith et al. 2019, Bomback et al. 2025a). In contrast, primary IC-MPGN is thought to be related to classical or lectin activation pathways due to the presence of IgG/IgM in the immune complexes found in the glomeruli (Smith et al. 2019). However, the mechanisms that lead to immune complex deposition remain incompletely understood (Bomback et al. 2025a). Acquired causes, such as autoantibodies that stabilise C3 or C5 convertase (e.g., C3 or C5 nephritic factors) might be involved in C3 dysregulation/overactivation in both IC-MPGN and C3G. Complement nephritic factors, which are autoantibodies that stabilise complement convertases and prolong their half-life, are reported in up to 50% of patients, which could drive C3 dysregulation in patients (van Schaik et al. 2024). Genetic variants in complement-related genes are identified in up to 20% of cases, however, familial cases are very rare (Iatropoulos et al. 2016, Fakhouri et al. 2020, Xiao et al. 2016).The C3 accumulation drives glomerular inflammation, mesangial expansion, capillary wall thickening, and progressive parenchymal damage, resulting in glomerulonephritis with proteinuria, haematuria, and occasionally nephrotic syndrome (Iatropoulos et al. 2016, Fakhouri et al. 2020, Anders et al. 2023). Persistent complement-mediated injury may lead to scarring, glomerulosclerosis, CKD, and irreversible kidney failure (Caravaca-Fontan et al. 2020b, Laurens et al. 2022, O'Keeffe et al. 2024, Pana et al. 2024). Although glomerular C3 deposition is universal, reduced serum C3 levels are observed in only about half of adult patients (Iatropoulos et al. 2016, Bomback et al. 2018, Tarragon Estebanez and Bomback 2024). C3G and primary IC-MPGN may be pathologically distinguished based on the composition of the glomerular deposits visualised using immunofluorescence (IF) of kidney biopsies (Cook and Pickering 2015). C3G is defined by dominant C3 staining and

minimal or absent immunoglobulin deposition, whereas IC-MPGN shows glomerular immune complex deposits containing both immunoglobulins and complement components (Bohlin et al. 1995, Bomback et al. 2025a, Cook and Pickering 2015, Fakhouri et al. 2010, Noris and Remuzzi 2024, Smith et al. 2019). Primary IC-MPGN is diagnosed when secondary causes, including autoimmune disease, chronic infection, or monoclonal gammopathy, have been excluded (Cook and Pickering 2015).

3.1.1.2 Symptoms of the Conditions and Patient Prognosis

The initial clinical presentation of C3G and primary IC-MPGN may range from asymptomatic/mild urinary abnormalities to advanced renal dysfunction (Fakhouri et al. 2020, Smith et al. 2019, Caravaca-Fontan et al. 2020b). Typically, patients present with non-specific symptoms of proteinuria and haematuria with preserved kidney function (Servais et al. 2012, Politano et al. 2020, Bomback et al. 2025a, Java and Fuller 2025).

Renal disease manifestations include micro- or macroscopic haematuria, light/heavy proteinuria, hypoalbuminaemia, reduced estimated glomerular filtration rate (eGFR), elevated serum creatinine and foamy urine (Servais et al. 2012, Bomback et al. 2018, Caravaca-Fontan et al. 2020b, Smith et al. 2019, Politano et al. 2020). Extra-renal manifestations may include acquired oedema, hypertension, infections, and less commonly, partial lipodystrophy and drusen-like deposits in the retina (like those seen in age-related macular degeneration but at an earlier age). Infections reported in patients with C3G/MPGN include urinary tract infections, upper respiratory tract infection, nasopharyngitis, and gastroenteritis, which is often a first sign of disease prior to diagnosis (Feldman D.L. 2018, Tyagi N. 2019, Caravaca-Fontan et al. 2020b, Sobi 2025a). Importantly, even after infection resolution, proteinuria and haematuria can persist (Ravindran et al. 2018). Infections may be recurrent and they vary in their frequency and severity (Feldman D.L. 2018). Moreover, fatigue, oedema, sleep disturbances and pain are substantial burdens impacting the vast majority of patients with C3G and primary IC-MPGN of which fatigue is the most frequently reported symptom (EURACTIV 2024, Lafayette et al. 2024a, Patry et al. 2024, Sobi 2024a, Sinha et al. 2025, Vendeville et al. 2025, Gopal et al. 2025).

C3G and primary IC-MPGN cause progressive, irreversible kidney damage that often leads to CKD and eventual kidney failure requiring dialysis or transplantation, with mortality about 21% higher than in the general population (Khandelwal et al. 2021, Nakagawa et al. 2018). CKD also greatly increases the risk of cardiovascular disease, which is the leading cause of death, especially in advanced stages (Yu et al. 2023, Jankowski et al. 2021). A significant proportion of patients, up to 70%, progress to kidney failure, with faster decline linked to higher proteinuria, while early reductions in proteinuria are associated with better kidney outcomes (Downward 2023, Chen et al. 2016, Marques et al. 2022). Even with treatment, long-term outcomes remain poor, as dialysis carries high mortality and kidney transplants frequently fail or experience disease recurrence (Wilson et al. 2019, Masoud et al. 2025, Tarragon et al. 2024).

3.1.1.3 Health-Related Quality of Life

Patients with C3G or primary IC-MPGN experience diminished health-related quality of life (HRQoL) (Lafayette et al. 2024a, Sinha et al. 2025), predominantly from the emotional (e.g., anxiety/depression) and physical (e.g., fatigue and pain) burdens associated with the conditions (Caravaca-Fontan et al. 2025b, Feldman et al. 2018, Lafayette et al. 2024a, Tyagi N. 2019). Other burdens that profoundly affect the lives of patients C3G or primary IC-MPGN and their caregivers include frequent healthcare visits and disruption of work and/or school (Caravaca-Fontan et al. 2025b, National Institute for Health and Care Excellence 2025, Rich et al. 2025, Tyagi N. 2019). Patient-reported outcome data highlighted a considerable detrimental impact on patient HRQoL, with more than half of all patients agreeing or strongly agreeing that the condition is a major problem in everyday life. Progression of C3G or primary IC-MPGN leading to CKD, dialysis, or transplantation further exacerbates the diminished HRQoL.

CKD has profound negative impact on HRQoL due to declining kidney function (Cruz et al. 2011, D'Arrigo et al. 2025). Multiple domains of HRQoL are impacted with patients often experiencing symptoms such as fatigue, pain, poor mobility, emotional distress, and poor sleep, which can severely limit daily activities and overall well-being (D'Arrigo et al. 2025, Fletcher et al. 2022, Krishnan et al. 2020, Cruz et al. 2011). Concurrently, the markedly elevated risk of cardiovascular events and cardiovascular comorbidity often associated with CKD adds a persistent layer of worry and health-related burden: knowing that heart disease risk is high tends to weigh on patients' sense of security and future health prospects (Guerra et al. 2021). Many patients report anxiety, depression or stress long before dialysis becomes necessary derived from living with a progressive, unpredictable disease as well as from constantly facing uncertainty about when and whether dialysis or transplantation will be required (Celano et al. 2016, Pagels et al. 2012, Alshelleh et al. 2022).

3.1.1.4 C3G and IC-MPGN Epidemiology

A comprehensive literature review on epidemiology of C3G and primary IC-MPGN conducted by Sobi (September 2025) summarised publications from 2010 to 2025 (Sobi 2025d). The review identified 11 studies providing estimates on the prevalence/incidence of C3G and primary IC-MPGN. From these publications, the reported incidence rates were:

- C3G (n=10 studies): 0.33 (95% CI 0.15, 0.51) per million
- Primary IC-MPGN (n=11 studies): 0.36 (95% CI 0.20, 0.52) per million.

Given the lack of direct literature on the prevalence of C3G and primary IC-MPGN, prevalence estimates are typically calculated from published incidence estimates. The estimated prevalence rates were:

- C3G (n=10 studies): 2.87 (95% CI 2.15, 3.59) cases per 100 000
- Primary IC-MPGN (n=11 studies): 2.27 (95% CI 1.68, 2.86) per 100 000

The most recent prevalence estimates for C3G and primary IC-MPGN are aligned with the EMA criteria for orphan drug designation (which includes disease prevalence of <5 per 10 000 people) (European Medicines Agency 2018). Pegcetacoplan was first granted orphan designation in the EU for the indication of C3 glomerulopathy on 18 December 2019 (EU/3/19/2201), and for C3 glomerulopathy with or without immune complexes, covering both C3G and primary IC-MPGN on 10 November 2022 (EU/3/22/2716).

3.1.2 Selected patient population

The relevant patient population for this application are patients aged 12 years or older with C3G or primary IC-MPGN. Based on input from a Nordic clinical expert, the combined prevalence of primary IC-MPGN and C3G in Denmark is estimated at around [redacted] patients with [redacted] to [redacted] new cases yearly (Sobi 2026). While patients have different ages of onset, most patients typically present with C3G or primary IC-MPGN in childhood or young adulthood. Based on the VALIANT trial, the average age is 25.97 years, approximately 43% of patients are male and the average weight is 63 kg (Fakhouri et al. 2025a). This was confirmed by a Nordic clinical expert as being relevant from a Danish perspective (Sobi 2026).

In Denmark, the yearly incidence of C3G and primary IC-MPGN is estimated at [redacted] cases per million, which corresponds to [redacted] to [redacted] cases yearly, based on Nordic clinical expert input (Sobi 2026). This aligns with the incidence reported in Noris and Remuzzi (2024) and Kovala et al. (2023), who reported an estimated yearly incidence of one to three cases per million. Furthermore, C3G is diagnosed more commonly than primary IC-MPGN, however, no detailed estimates exist (Sobi 2026). The incidence in Denmark is considered stable.

The calculation for the expected number of patients considered to be treated from Table 1 is illustrated in Figure 1 for Year 5.

The prevalent population for C3G and IC-MPGN in Denmark is estimated at [redacted] (diagnosed and undiagnosed), based on dialogue with clinical experts (Sobi 2025b). Approximately 75% of prevalent patients are assumed to be diagnosed in Denmark, resulting in [redacted] patients. Diagnosis of C3G and primary IC-MPGN is biopsy-dependent and requires expert interpretation to distinguish complement-mediated disease from immune complex-mediated or secondary MPGN. A review of a Dutch Nationwide Pathology Databank described persistent diagnostic gaps and misclassification. Since no Danish data exists it is assumed that this situation is also relevant in Denmark and will remain so until treatment for these diseases is more firmly embedded in routine clinical setting in Denmark (Overwijk et al. 2026). Of diagnosed patients, [redacted]% are assumed to receive systemic treatment, resulting in [redacted] patients. This assumption is anchored in multinational real-world evidence consistently showing that approximately 82-83% of patients with C3G are receiving pharmacological treatment once diagnosed. The [redacted]% represent a rounded, Denmark-scenario assumption (Sinha et al. 2025). Furthermore, among treated patients, [redacted]% are assumed to remain uncontrolled and therefore complement inhibitor-eligible, resulting in [redacted] patients. Real-world studies consistently demonstrate persistent disease activity despite systemic therapy. In a large multinational real-world study, 68.9% of treated patients with available data had proteinuria ≥1 g/day,

a commonly used marker of ongoing disease activity in C3G and primary IC-MPGN. Other multinational real-world datasets report similar proportions (~60-70%) of treated patients with clinically relevant residual proteinuria (Sinha et al. 2025, Sobi 2025a). Moreover, patients under 12 years are not within the indication and there is an expected drop-off due to advanced kidney failure (CKD5). Moreover, it is expected that there are other complement mediating treatments available for Danish patients. Therefore, only approximately XX% of the XXX patients are expected to receive pegcetacoplan in Year 5 at full patient uptake (Figure 1 and Table 1). Currently, XXX patients are treated with pegcetacoplan in Denmark, and XXXX new patients are expected to start treatment in case of reimbursement approval, resulting in XXX patients in Year 1. For Year 2, it is expected that another XXXX patients will start treatment, resulting in XXX patients. After that, additional patient uptake is expected to slow down (XXX additional patients in Year 3) since new alternative treatment options for C3G and primary IC-MPGN are expected to be introduced in Denmark. Following this rationale, XXX patients are expected in Year 4 before reaching full patient uptake in Year 5 (XXX patients).

Figure 1. Estimated number of patients at year 5

Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis

Table 1. Expected number of patients and patient uptake of the intervention

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number of patients*	XXX	XXX	XXX	XXX	XXX
Patient uptake**	XX%	XX%	XX%	XX%	XX%

*The number of patients in Denmark eligible for the new treatment in accordance with the EMA indication, minus the number of patients who are not considered suitable for treatment (e.g., due to age or comorbidity), and minus those who are expected to decline treatment. As a general rule, the number of new (incident) patients per year should be used. However, if prevalent patients are expected to be offered treatment, these should be included in year 1. **Patient uptake is defined relative to the expected number of eligible patients. If full patient uptake (100%) is not expected from year 1 due to a gradual implementation, the relevant percentage uptake must be specified for each year. Once the new treatment is expected to be fully implemented, patient uptake must reach 100% (no later than year 5). For definitions of patient numbers and patient uptake, see the Danish Medicines Council's guideline on budget impact analysis.

3.2 Intervention

Table 2. Overview of the intervention

Therapeutic indication relevant to the assessment	Aspaveli is indicated for the treatment of adult and adolescent patients aged 12 to 17 years with C3G or IC-MPGN in combination with a RAS inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated.
Generic name	Pegcetacoplan
ATC code	L04AJ03
Mechanism of action	Pegcetacoplan binds to complement protein C3 and its activation fragment C3b, inhibiting the cleavage of C3. Pegcetacoplan further inhibits the C5 convertase, prevents the formation of C3b deposition on cell surfaces and production of inflammatory fragments C3a and C5a.
Administration method	Aspaveli is self-administered via a subcutaneous syringe system infusion pump.
Packaging type, pack sizes, shelf life and strengths	Carton with one or eight glass vials Shelf life: 30 months in a refrigerator and protected from light Strength: 54 mg/mL
Package size(s)	1080 mg, 20 mL single-dose vial, 1-unit pack and 8-unit pack.
If vials: Can these be shared?	No vial sharing.
Pre-medication: Should pre-medication be administered? Which one?	Patients should be vaccinated against *Streptococcus pneumoniae*, *Neisseria meningitidis* serogroup A, C, W, Y, and B, and *Haemophilus influenzae* type B at least 2 weeks prior to receiving pegcetacoplan. If immediate therapy with pegcetacoplan is indicated, the required vaccines should be administered as soon as possible, and the patient should be treated with appropriate antibiotics until 2 weeks after vaccination.
Co-administration: Should the drug be administered with other drugs? Which ones?	Co-administration with RAS inhibitors according to the indication.
Need for diagnostics, monitoring or other tests (e.g., *companion diagnostics*)	All patients must be monitored for early signs of infections caused by encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae*.

Table 3. The intervention in the clinical study and in the health economic model

	Clinical study	Health economic model
Dosage and frequency	The recommended dose of Aspaveli for the treatment of C3G or primary IC-MPGN is 1080 mg for adults or adolescents >50 kg and weight-based dosing for adolescents <50 kg (35 to <50 kg – 648 mg [first dose], 810 mg [second dose and maintenance dose]; 30 to <35 kg – 540 mg [first and second dose], 648 mg [maintenance dose]) twice weekly (administered on Day 1 and Day 4 of a treatment week).	1080 mg twice weekly
Average dose	1048.39 mg	1080 mg
Criteria for treatment discontinuation	In the study, participants were allowed to discontinue for any reason. Treatment needs to be discontinued in case of hypersensitivity.	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. This assumption was verified by a Nordic clinical expert (Sobi 2026). Patients who achieve stable disease pause pegcetacoplan treatment during time in stable disease, which was described as the best possible approach by a Nordic clinical expert (Sobi 2026).
Treatment duration	Median: 176 days Mean (SD): 171.3 (26.08) days	9.91 years
Dose adjustment: Report if/how dose adjustment is made*	Doses were adjusted accordingly if patients switched between weight categories[#]	N/A
Dose pause: Specify if/how pause(treatment interruption) is performed*	No treatment interruptions.	See above in table: treatment pause during time in stable disease

* If the Relative Dose Intensity (RDI) for dose adjustment and/or pause is used, include definition of RDI, see the Danish Medicines Council's guideline for calculating costs.

One adolescent patient dropped below 50 kg, but dose of 1080 was maintained.

In the VALIANT trial, the dosage patients received were weight-based as described in Table 3, whereas in the model, 1080 mg twice weekly was used in line with the average age used in the model (see Table 10). Below, the weight- and dose distribution from the latest pre-specified data cut (12 February 2025) in the clinical study is shown in Table 4 and Table 5. No differences are expected between the dose distribution in Danish clinical practice and the clinical trial.

Table 4. Baseline weight distribution in the VALIANT trial

Baseline weight distribution			
Weight	Pegcetacoplan	Placebo	Total
30 to <35	[redacted]	[redacted]	[redacted]
35 to <50	[redacted]	[redacted]	[redacted]
>50	[redacted]	[redacted]	[redacted]

Table 5. Number of doses and average dose given per arm and per population in the VALIANT trial

Total population						
Weight	Number of doses			Average dose (mg)		
	Pegcetacoplan	Placebo	Total	Pegcetacoplan	Placebo	Total
30 to <35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35 to <50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adolescents						
Weight	Number of doses			Average dose (mg)		
	Pegcetacoplan	Placebo	Total	Pegcetacoplan	Placebo	Total
30 to <35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35 to <50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adults						

Weight	Number of doses			Average dose (mg)		
	Pegcetacoplan	Placebo	Total	Pegcetacoplan	Placebo	Total
30 to <35	XX	XX	XXX	XXXX	XXXX	XXXX
35 to <50	XXX	XX	XXX	XXXX	XXXX	XXXX
>50	XXXX	XXXX	XXXX	XXXXXX	XXXXXX	XXXXXX

Note: Adolescents with weight 30 to <35 kg: Two (first and second) loading doses of 540 mg; Maintenance doses 648 mg; No deviation noticed in data.

Adolescents with weight 35 to <50 kg: Loading (first) dose of 648 mg; Maintenance dose 810 mg; There were XX loading doses for patients moving from placebo-to-pegcetacoplan; One patient received XXXXXXXXXXXXX mg; XXX patient(s) who were >50 kg at the beginning of the study dropped below threshold for some time during study. The patient(s) XXXXXXXXXXXXXXXXXXXXXXXXX mg doses during that period (no reduction in dose was done; XXX patient(s) started with weight <35 kg, when weight got higher the threshold dose was adjusted for 35 to <50 kg (XXX mg)).

Adolescents with weight >50 kg: Normal dose was 1080 dose; XXX patient(s) received XXX XXXX mg dose(s); XXX patient(s) received XXX XXX mg dose(s)

Adults with weight >50 kg: XXX patient(s) received XXX XXX mg dose(s), this might potentially be error in reporting (missing 0); XXX patient(s) received XXX XXX mg dose(s); XXX dose(s) of X mg is reported

Source: (Sobi 2025c)

3.2.1 Mechanism of Action

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b, thereby inhibiting the cleavage of C3 and the generation of downstream effectors of complement activation. Moreover, pegcetacoplan prevents the formation of C3b deposition on cell surfaces, the main pathophysiological driver in C3G and primary IC-MPGN. Clearance of C3 deposits in the glomeruli is the first sign to confirm the pathological mechanism has stopped and that therapy is not only addressing symptoms. Furthermore, pegcetacoplan blocks the production of the inflammatory fragments, C3a and C5a, that are driving inflammation and recruiting immune cells. It also inhibits the C5 convertase and consequently the assembly of the membrane attack complex, a structure that causes cell damage.

By targeting both C3 and C3b, pegcetacoplan provides broad inhibition of all three activation pathways (classical, lectin, and alternative) and modulates the overactivation of the complement system.

3.2.2 The Intervention in the Context of Danish clinical practice

The management of C3G and IC-MPGN in Denmark is guided by the recommendations from the Danish Society of Nephrology (DNS 2023b), which are themselves based on the 2021 KDIGO guidelines (Rovin et al. 2021). The focus has traditionally been on addressing complications such as proteinuria, hypertension, hyperlipidaemia, and oedema associated with glomerular and CKD. For IC-MPGN it is suggested to treat patients with

either cyclophosphamide, mycophenolate, calcineurin-inhibitors, or rituximab in addition to prednisolone for 3 to 6 months (DNS 2023b).

3.2.2.1 Current Treatment Guidelines

According to guidelines, treatment decisions in C3G and IC-MPGN should be individualised. In patients with mild disease, defined by stable or only mildly impaired renal function and mild to moderate proteinuria, a conservative, renoprotective approach is recommended. This includes optimised blood pressure control, reduction of proteinuria through RAS blockade, and general kidney-protective measures. In patients with progressive renal insufficiency or a nephrotic-range proteinuria, immunosuppressive or complement-targeted therapy may be considered. When autoantibodies such as C3 nephritic factor or anti-factor H antibodies are detected, a combination of glucocorticoids and mycophenolate mofetil (MMF) is recommended. If a genetic defect in complement regulation is identified, therapy may include immunosuppression or, in selected cases, complement blockade (e.g., C5 inhibition or other pathway-specific inhibitors). In patients with deficiency of complement regulatory proteins, plasma infusion or plasma exchange with fresh frozen plasma can be considered to restore complement control (DNS 2023b).

The current KDIGO guidelines for glomerular diseases including C3G and primary IC-MPGN, which were published in 2021, suggest the following treatment approach (Rovin et al. 2021):

- For patients with C3G:
    - Usual supportive measures are encouraged for patients with glomerular disease (e.g., dietary and lifestyle management, maximal tolerated or approved doses of renin-angiotensin-aldosterone system [RAAS] inhibitors).
    - Consider immunosuppressive therapies (glucocorticoids with or without MMF) for patients with proteinuria >1 g/day and haematuria or who have had declining kidney function for ≥6 months.
    - Use of eculizumab can be considered in cases of progressive disease and failure to respond to other therapies; however, the benefits of eculizumab remain unestablished.
- For patients with primary IC-MPGN:
    - Supportive therapy alone with RAAS inhibition alone is suggested for proteinuria <3.5 g/day in the absence of nephrotic syndrome, and a normal eGFR.
    - A limited treatment course of glucocorticoids is recommended for patients with nephrotic syndrome, and normal or near-normal serum creatinine.
    - Adding glucocorticoids and immunosuppressive therapy to supportive care is recommended for patients with abnormal kidney function (but without crescentic involvements), active urine sediment, with or without nephrotic-range proteinuria.

- For most patients with primary IC-MPGN presenting with an eGFR <30 ml/min per 1.73 m^2, treat with supportive care alone.

- Patients with either C3G or primary IC-MPGN who fail to respond to the treatment approaches should be considered for a clinical trial where available or should be treated conservatively with referral for kidney transplant evaluation in due course unless kidney biopsy shows any reason that could support immunosuppression.

Selected KDIGO advising experts provided additional considerations for the management of C3G and primary IC-MPGN in children. Their suggested approach largely agrees with the 2021 KDIGO guidelines for adults, but with a more aggressive threshold for initiating therapy at >0.5 g/day of proteinuria and additional emphasis on tapering steroids and immunosuppressants. Their guidelines for management in children are presented in Vivarelli et al. (2022).

3.2.2.2 Expected use in the treatment pathway

In Denmark, treatment of C3G and primary IC-MPGN has historically been based on supportive care and off-label immunosuppression, as no disease-specific therapies were previously available, as described in Section 3.2.2.1. Therefore, Aspaveli in combination with RAS inhibitor (in line with its indication) is anticipated to become the preferred first-line treatment option after diagnosis in addition to supportive care, given its targeted mechanism addressing the underlying disease pathology (see Section 3.2.1). Conventional therapies are expected to play an adjunctive or supportive role rather than forming the core of first-line disease-modifying treatment.

3.2.2.3 Unmet Need

Currently, there are no disease-modifying therapies that address the underlying drivers of C3G and primary IC-MPGN, resulting in patients having irreversible loss of kidney function (Noris and Remuzzi 2024, KDIGO 2024). Symptomatic treatments have limited impact on disease progression due to the progressive nature of the disease and come with meaningful side effects (Noris and Remuzzi 2024, KDIGO 2024). As such, supportive treatment options i.e. ACE/ARBis, immunosuppressive therapies, and steroids have not shown to reliably stop disease progression (Noris and Remuzzi 2024, KDIGO 2024). So far, dialysis and kidney transplants are the only options for patients who reach kidney failure but are also associated with significant mortality. Kidney transplants are not curative in C3G and primary IC-MPGN due to high rates of recurrence and subsequent allograft loss (Himmelfarb et al. 2020, Robinson et al. 2014, Wilson et al. 2019, O'Shaughnessy et al. 2017, Smith et al. 2019, Tarragon et al. 2024). Additionally, given the lack of targeted treatment options available for C3G and primary IC-MPGN, there are similarly no treatment options for patients who recur post-transplant (Smith et al. 2019, Regunathan-Shenk et al. 2019, Angelo et al. 2011, Goodship et al. 2017). Based on this, and according to the indication, pegcetacoplan should be used as a first-line treatment, targeting the underlying drivers of C3G and primary IC-MPGN, in combination with renin-angiotensin system (RAS) inhibitors that reduce proteinuria, unless RAS inhibitor treatment is not tolerated or contraindicated (EMA 2026). Using pegcetacoplan and RAS

inhibitors together targets two different processes that contribute to disease progression, i.e. hemodynamic stress and immunologic damage.

A substantial unmet medical need remains due to the persistent shortage of donor kidneys. The number of patients with end-stage renal disease eligible for transplantation continues to exceed the supply of available organs, resulting in prolonged waiting times, extended periods on dialysis, and avoidable morbidity and mortality. Limited kidney availability restricts access to the clinically preferred treatment and contributes to reduced quality of life, lower survival rates compared with transplantation, and considerable healthcare and societal costs (GOS 2025a, GOS 2025b, Vävnadsrådet 2020). Kidney transplantation can temporarily restore renal function, but it does not address the underlying complement dysregulation in C3G and primary IC-MPGN (Pickering et al. 2013). Consequently, recurrence of disease in the transplanted kidney is common, often leading to graft dysfunction and graft loss (Koirala et al. 2025, Guzman and Perry 2025). Thus, the scarcity of kidneys for this patient group is compounded by the lack of effective disease-modifying therapies that can prevent recurrence and protect the transplanted organ.

3.2.3 Advanced Therapy Medical Products

Not applicable.

3.3 Choice of Comparator(s)

No approved active treatment is currently available for C3G or IC-MPGN. The off-label treatments mentioned in the KDIGO guidelines and Danish guidelines for C3G and primary IC-MPGN, i.e. glucocorticoids, MMF, RAAS inhibitors, cyclophosphamide, rituximab, or eculizumab, have not been assessed for cost-effectiveness in this patient population. Furthermore, the factor B inhibitor iptacopan is approved only for C3G in adults and has not been assessed for cost-effectiveness by the DMC (request withdrawn 18 December 2025) (DMC 2025). Hence there is no active treatment comparator applicable to this case, consequently the most relevant comparison to determine the cost-effectiveness of pegcetacoplan in C3G and IC-MPGN is pegcetacoplan with standard of care (SoC) versus SoC with no active treatment (referred to as SoC only from here on).

SoC in this context consists of non-disease-specific agents including ARBs and ACE inhibitors, SGLT-2 inhibitors, and immunosuppressive therapy. Patients with C3G or IC-MPGN often take several medications to handle potential symptoms and progression-related complications. The agents which help manage those symptoms have been validated as comprising SoC in Danish clinical practice (DNS 2023b, DNS 2023a). SoC is accordingly a bundle of treatments rather than a single pharmaceutical.

Table 6 and Table 7 are not applicable.

Table 6. Overview of the comparator

Therapeutic indication relevant to the assessment
Generic name
ATC code
Mechanism of action
Administration method
Packaging type, pack sizes, shelf life and strengths
Package size(s)
If vials: Can these be shared?
Pre-medication: Should pre-medication be administered? Which one?
Co-administration: Should the drug be administered with other drugs? Which ones?
Need for diagnostics, monitoring or other tests (e.g., *companion diagnostics*)

Table 7. Comparator in the clinical study and in the health economic model

	Study	Health economic model
Dosage and frequency		
Average dose		
Criteria for treatment discontinuation		
Treatment duration		
Dose adjustment: Report if/how dose adjustment is made*		
Dose pause: Specify if/how pause (treatment interruption) is performed*		

	Study	Health economic model
Dosage and frequency		

* If RDI for dose adjustment and/or pause is used, include definition of RDI, see the Danish Medicines Council's guideline for calculating costs.

3.4 Subsequent Treatment

Pegcetacoplan is the first disease-specific, complement-targeted treatment approved for the treatment of C3G and primary IC-MPGN. There are currently no established subsequent lines of therapy following pegcetacoplan and therefore, represents the primary and only approved targeted treatment option for patients with C3G and primary IC-MPGN.

Accordingly, Table 8 is not applicable.

Table 8. Assumptions regarding subsequent treatment in the health economic analysis

Subsequent treatment	[Intervention] %	[Comparator] %	Average treatment duration including source	Dosage (Dose, frequency and form of administration including source)	Any assumptions regarding dose adjustment and pause including source

3.5 Relevant Outcomes

3.5.1 Definition of Outcomes

In the VALIANT trial, endpoints selected reflect measures with documented associations to disease severity and progression.

Reduction in urinary protein-to-creatinine ratio (uPCR) is widely used because proteinuria quantitatively correlates with glomerular injury and progression risk; decreases in proteinuria have been linked to better long-term kidney outcomes in both C3G and IC-MPGN cohorts (Caravaca-Fontán et al. 2025). A composite endpoint of improved eGFR and reduction in uPCR captures both preservation or enhancement of kidney function and reduction of active injury, addressing two key aspects of clinical benefit. Expert workgroups evaluating trial endpoints in C3G have recommended that favourable effects across proteinuria and eGFR measures provide convincing evidence of efficacy (Nester et al. 2024). A uPCR reduction ≥50% is considered a meaningful threshold, as greater reductions in proteinuria over time are independently associated with slower eGFR decline and a lower risk of kidney failure (Caravaca-Fontán et al. 2025).

Measuring the difference in mean change of eGFR between treatment groups directly assesses kidney function trajectory. Longitudinal changes in eGFR remain one of the strongest predictors of progression to kidney failure in glomerular diseases, including C3G (Caravaca-Fontan et al. 2023). Finally, the proportion of patients with a decrease in C3c staining on renal biopsy serves as a histologic indicator of reduced complement deposition, the fundamental pathologic hallmark of these diseases. Serial changes in glomerular C3 staining have been examined in emerging trials as evidence that targeted therapy may alter core disease pathology (Nester et al. 2024).

Table 9. Outcomes

Outcome	Follow-up time	Definition
Reduction in uPCR (proteinuria) compared to baseline VALIANT (NCT05067127)	Week 26, Week 52	Difference in mean change of log-transformed uPCR from baseline to Week 26/52 (measured by equal-weighted average over weeks 24, 25, and 26/50, 51, and 52) between the pegcetacoplan group and the placebo group.
Proportion of patients achieving composite renal endpoint compared to baseline VALIANT (NCT05067127)	Week 26, Week 52	Defined as (1) a stable or improved estimated glomerular filtration rate (eGFR) compared to baseline (≤15% reduction in eGFR), and (2) a ≥50% reduction in uPCR compared to baseline.
Proportion of patients achieving a uPCR reduction ≥50% compared to baseline VALIANT (NCT05067127)	Week 26, Week 52	Defined as the number of patients with a ≥50% reduction in uPCR compared to baseline.
Adjusted mean difference in mean change of eGFR compared to baseline VALIANT (NCT05067127)	Week 26, Week 52	Difference in mean change of eGFR from baseline to Week 26/52 between the pegcetacoplan group and the placebo group.
Proportion of patients with decrease in C3c staining at Week 26 compared to baseline VALIANT (NCT05067127)	Week 26, Week 52	Subject who showed decrease in C3c staining was defined as decrease of at least two orders of magnitude of intensity from baseline.

Abbreviations: C3c, complement 3 component; eGFR, estimated glomerular filtration rate; uPCR, urine protein creatinine ratio

Source: (Sobi 2025c, Sobi 2024a)

3.5.2 Relevance of Outcomes

According to Nester et al. (2024), a favourable treatment effect on proteinuria, eGFR, and histopathology together provides convincing evidence of efficacy in the setting of a therapy that targeted the complement pathway.

Change in uPCR

uPCR measurements are a reliable tool to assess and quantify proteinuria, which serves as a critical indicator of disease activity, prognosis, and treatment success (Haider and Aslam 2025, Thompson et al. 2019). Persistent proteinuria in C3G and IC-MPGN is one of the strongest predictors of renal disease progression and eventual kidney failure. Accordingly, a reduction of >50% in uPCR is considered strongly representative for renal improvement (Inker et al. 2014, Marques et al. 2022, Caravaca-Fontan et al. 2022). Modest uPCR values (0.44 g/g to 0.88 g/g) are associated with high risks of kidney failure within 10 years, and even uPCR values below 0.44 g/g still confer a 20% risk (Pitcher et al. 2023). More recently, over time proteinuria was associated with an increased risk of kidney function decline (Ghaddar et al. 2025).

Change in eGFR

eGFR serves as a fundamental measure of kidney function and plays a pivotal role in prognosis, risk stratification, treatment response, and clinical decision-making in other glomerular diseases, such as IgAN (Selvaskandan et al. 2020, Knoop et al. 2015). UK RaDaR Registry data suggest that stabilising or slowing eGFR decline for at least six months could benefit patients with C3G or primary IC-MPGN (Masoud et al. 2024).

Histopathology (decrease in C3c staining)

C3G is defined by the predominant deposition of complement components, and C3 deposition is believed to play a causal role in the disease (Smith et al. 2019). Clinically, a reduction in C3c staining indicates that the investigational therapy is modifying the underlying disease process rather than only improving symptoms or laboratory surrogates and is therefore interpreted as histological evidence of reduced disease activity and potential stabilisation of renal pathology (Nester et al. 2024).

3.5.3 Validity of Outcomes

The validity of outcomes was evaluated to ensure the credibility and generalisability of the study, ensuring the potential of evidence-based decision-making and avoiding misinterpretations. For the VALIANT study, the change in uPCR, change in eGFR, and decrease in C3c were validated.

Change in uPCR

Proteinuria was previously validated as a valid endpoint for nephrology studies by the Food and Drug Administration (FDA) (FDA 2025), which was further shown for C3G and IC-MPGN (Caravaca-Fontán et al. 2025, Masoud et al. 2025).

Change in eGFR

eGFR was described as a valid surrogate endpoint in C3G by the Kidney Health Initiative C3 Glomerulopathy Trial Endpoints Work Group (Nester et al. 2024). This was further confirmed by the FDA and EMA, who accepted the eGFR slope as a valid surrogate endpoint describing the rate of change of eGFR over time (Sugawara et al. 2024).

Composite endpoint

An inverse relationship between the slope of eGFR and the change of proteinuria over time during renal disease progression was described by Caravaca-Fontan et al. (2022), justifying the use of a composite endpoint consistent of a ≤15% reduction in eGFR and a ≥50% reduction in uPCR. This was further supported by findings from Nuijten et al. (2009), Marques et al. (2022) and Troost et al. (2021).

Histopathology (decrease in C3c staining)

Change in C3c was previously discussed as a surrogate endpoint by the Kidney Health Initiative C3 Glomerulopathy Trial Endpoints Work Group and was considered valuable in determining C3 activation inhibition (Nester et al. 2024). A Delphi consensus study further determined that the removal of kidney C3 deposits serves as a key endpoint, demonstrating that the treatment effectively targets the underlying cause of C3G and IC-MPGN (Caravaca-Fontán et al. 2025). In the VALIANT study, a decrease in staining intensity of at least two orders of magnitude from baseline was required to be considered significant. C3c staining intensity was determined on a scale of 0 to 3 (including 0, trace, 1+, 2+, 3+) (Pickering et al. 2013).

4. Health economic analysis

4.1 Reference-case Assumptions

Table 10. Reference-case assumptions in the health economic analysis

Assumption regarding	Assumption	Justification
Patient population	Adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated. The modelled baseline distributions of CKD stages	Therapeutic indication as defined by EMA.

Assumption regarding	Assumption	Justification
	and uPCR levels were based on patient-level data from the VALIANT trial and confirmed to be in line with the Danish prevalent patient population by a Nordic clinical expert (Sobi 2024a, Sobi 2026).	
Intervention	Pegcetacoplan with standard of care	
Comparator(s)	SoC with no active treatment	
Clinical outcomes	uPCR eGFR	
Analysis type	Cost-utility	To capture the superior effect of pegcetacoplan compared to SoC only
Model type	Markov model	
Average age at entry into the model	26 years	Based on patient-level data from the VALIANT trial
Time horizon	Lifetime (74 years)	C3G and IC-MPGN are lifelong glomerular diseases; therefore, a lifetime time horizon (up to 100 years of age) was used to capture all health benefits and costs in line with DMC guidelines.
Cycle length	3 months	Considered 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 of disease progression.
Half-cycle correction	Yes	To improve accuracy

Abbreviations: C3G, C3 glomerulopathy; DMC, Danish Medicines Council; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; IC-MPGN, primary immune-complex membranoproliferative glomerulonephritis; uPCR, urine protein creatinine ratio

References: (Sobi 2024a, Sobi 2026)

4.2 Model Type and Model Structure

In Table 11, an overview of the health economic analysis and model structure is provided.

Table 11. Choice of health economic analysis, model, and model structure

Health economic analysis	Model type	Model structure	Assumptions
Cost-utility analysis	Markov model	23 health states representing the cohort's uPCR and CKD stage (eGFR level) or correspond to stable disease, dialysis, transplant, or death	Patients who progress to CKD stage 5, require dialysis, or are in the stable disease state do not receive pegcetacoplan treatment (section 4.2.1) The model captures the reduced need for kidney transplants with pegcetacoplan treatment using an opportunity cost approach. This is implemented by generating additional cost savings and QALY gains due to other patients receiving a transplant instead of remaining on dialysis (Section 9.5.1).

A cost-utility analysis is used to capture the superior effect of pegcetacoplan compared to SoC only. The model used is a Markov model with 23 health states representing the cohort's uPCR and CKD stage (eGFR level) or correspond to stable disease, dialysis, transplant, or death (see Section 3.1.1.1 and Section 3.1.1.2). A Markov cohort model is appropriate because the disease follows a progression through discrete, mutually exclusive health states that patients transition between over time. In addition, the Markovian assumption is seen as a reasonable approximation for disease progression. Specific utilities and costs are associated with all health states. uPCR ranges were used as the primary basis for defining health states, based on findings identifying uPCR as a key predictor of disease progression in the model population (Section 3.5.2). To more accurately reflect the severity and progression of CKD, eGFR levels were incorporated as a second defining variable, drawing on the structure of existing CKD models.

At the start of the model, patients are assigned to uPCR health states and CKD stages based on trial data and enter the simulation either receiving pegcetacoplan treatment or

not. Pegcetacoplan is administered as an add-on to SoC. At each cycle, patients transition between uPCR health states and CKD stages according to probabilities derived from clinical trial data. Specifically, the rate of eGFR decline, and thus progression through CKD stages, is driven by uPCR levels, with higher uPCR associated with more rapid kidney function deterioration (Section 3.5.2).

The model also accounts for the possibility of disease stabilisation. While disease stabilisation slows the decline of eGFR, it does not reverse existing kidney damage. Achieving stable disease is possible only for patients with uPCR <0.5 g/g, in line with input from a Nordic clinical expert in nephrology (Sobi 2025e). This threshold is used in other kidney diseases as the cut-off for when a patient is considered to be in complete remission (Pitcher et al. 2023). 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 pause treatment with pegcetacoplan but stay on BSC while in stable disease and resume pegcetacoplan therapy upon disease relapse to maintain low uPCR levels. Once in stable disease, patients' proteinuria would in clinical practice be monitored to ensure that treatment is re-initiated if their uPCR level exceeds 0.5 g/g. In the model, the average time patients' disease is assumed to stay stable is XXXXXXXXX (Section 9.3.3).

As the disease progresses, continued eGFR decline can result in ESKD, necessitating dialysis or kidney transplantation for survival. Dialysis and transplant are treated as separate health states within the model. After transplantation, patients transition to post-transplant health states 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 dialysis or a second transplant (Section 3.5). For post-transplant patients who do not achieve stable disease, pegcetacoplan treatment is re-initiated.

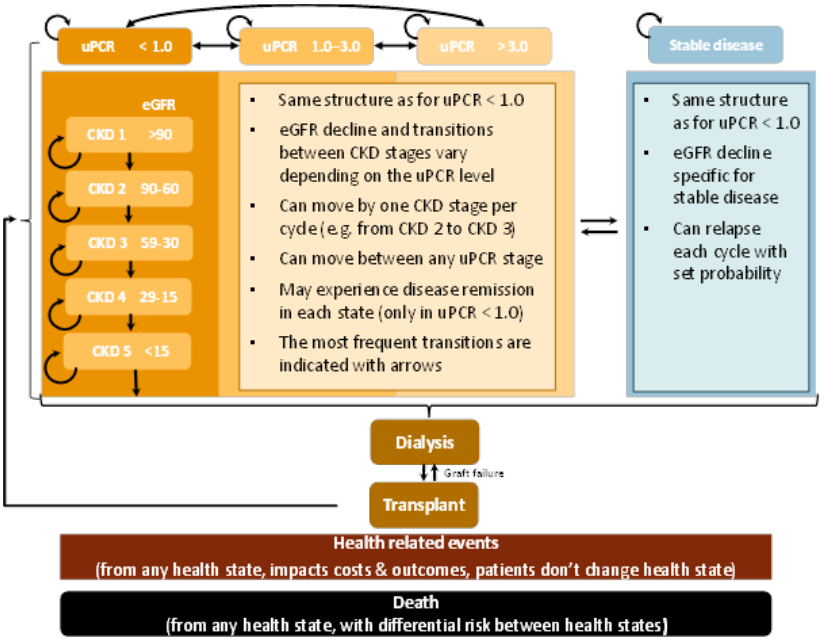
Pegcetacoplan treatment impacts disease progression by reducing uPCR levels, which slows the decline in eGFR and delays advancement through CKD stages. Furthermore, patients receiving pegcetacoplan have a higher probability of disease stabilisation compared to those on standard care, due to achieving lower uPCR levels and a greater proportion reaching uPCR <0.5 g/g.

A further long-term benefit of pegcetacoplan is the reduced need for kidney transplants, freeing up kidneys for other patients on the waiting list. The model captures this opportunity cost effect, generating additional cost savings and QALY gains due to patients receiving a transplant instead of remaining on dialysis (Section 9.5.1). A Nordic clinical expert confirmed that such reduced transplant demand would shorten waiting times, supporting the inclusion of these broader health system benefits (Sobi 2026).

The model also captures the increased risk of mortality and other health events, with associated disutilities, related to later CKD stages (section 8.1).

A graphical representation of the model structure is shown in the Figure 2 below.

Figure 2. Structure of the model



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uPCR, urine protein creatinine ratio

4.2.1 Treatment Discontinuation

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. This assumption was verified by a Nordic clinical expert (Sobi 2026). Patients who achieve stable disease also pause pegcetacoplan treatment during time in stable disease, which was described as the best possible approach by a Nordic clinical expert (Sobi 2026).

In addition, during the overall study period (week 0-52), X/XX=XX% of the study participants in the pegcetacoplan arm discontinued treatment. This share was converted to a probability of discontinuation using the following calculation:

Assuming discontinuation follows an exponential distribution

Annual risk: p_year = XXXX

Convert to rate: λ = -ln(1 - XXXX) = -ln(XXXX) = XXXX

3-month probability (1/4 of a year):

p_quarter = 1 - e^(-λ/4) = 1 - e^(XXXX) ≈ XXXX%

I.e. XXXX% per 3-month cycle.

The same probability of discontinuation is assumed during the whole model time horizon.

Discontinuation of individual components of standard care is reflected in the treatment distribution observed in the VALIANT trial.

5. Literature Review

5.1 Literature Used to Assess Clinical Effectiveness and Safety

Table 12. Relevant literature included in the assessment of effectiveness and safety

Reference	Study name	NCT number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
Fakhouri F, Bomback AS, Ariceta G, Delmas Y, Dixon BP, Gale DP, Greenbaum LA, Han SH, Isbel N, Le Quintrec M, Licht C, Mastrangelo A, Mizuno M, Neves de Holanda MI, Pickering MC, Remuzzi G, Van De Kar N, Vivarelli M, Walker PD, Wallace D, Zecher D, Francois C, Deschatelets P, Li L, Wang Z, Abad-Franch L, Kinnman N, López-Lázaro L, Szamosi J, Nester CM; VALIANT Trial Investigators Group. Trial of Pegcetacoplan in C3 Glomerulopathy and Immune-Complex MPGN. N Engl J Med. 2025 Dec 4;393(22):2210-2220. doi: 10.1056/NEJMoa2501510. (Fakhouri et al. 2025b) Data on file Unpublished data 2024: VALIANT Clinical Study Report (Sobi 2024a)	VALIANT	NCT05067127	Start: 12/11/21 Completion: 14/01/25 Data cut-off: 20/06/24 Data lock date: 12/02/25	Pegcetacoplan vs placebo in patients with C3G or IC-MPGN.

Reference	Study name	NCT number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
Data on file Unpublished data 2025: VALIANT Clinical Study Report (Sobi 2025c)				

*List all study publications and state for each which comparison they are used for.

Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, primary immune-complex membranoproliferative glomerulonephritis

5.2 Literature Used to Assess Health-Related Quality of Life

Table 13. Relevant literature included in the assessment of health-related quality of life

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in paragraph
Hvidberg MF, Petersen KD, Davidsen M, Witt Udsen F, Frolich A, Ehlers L, et al. Catalog of EQ-5D-3L Health-Related Quality-of-Life Scores for 199 Chronic Conditions and Health Risks in Denmark. MDM Policy Pract. 2023;8(1):23814683231159023. (Hvidberg et al. 2023)	EQ-5D-3L, for the disutility of myocardial infarction, stroke, and heart failure	Desk research	Section 10.4.4
Cooper JT, Lloyd A, Sanchez JJG, Sörstadius E, Briggs A, McFarlane P. Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. Health	EQ-5D-3L, for utilities of CKD stages 3,4, and 5, and for utilities for haemodialysis, peritoneal dialysis, and transplant	Desk research	Section 10.4.1

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in paragraph
Qual Life Outcomes. 2020 Sep 21;18(1):310. doi: 10.1186/s12955-020-01559-x. (Cooper et al. 2020)			
Torkilseng EB, Clarke N, Sopina L, Oddershede L, Wolf RT, Lawrance R, Trigg A, Bennett B, Shaw JW. Predicting Danish EQ-5D-5L Utilities Based on United Kingdom EQ-5D-3L Utilities for Use in Health Economic Models. Pharmacoecon Open. 2025 May;9(3):433-443. doi: 10.1007/s41669-025-00562-6. Epub 2025 Feb 22. (Torkilseng et al. 2025)	Mapping from EQ-5D-3L UK tariff to EQ-5D-5L DK tariff	Desk research	Section 10.4.4; Appendix G.3

5.3 Literature Used as Input in the Health Economic Model

Table 14. Relevant literature used in the health economic model

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
Hvidberg MF, Petersen KD, Davidsen M, Witt Udsen F, Frolich A, Ehlers L, et al. Catalog of EQ-5D-3L Health-Related Quality-of-Life Scores for 199 Chronic Conditions and Health Risks in Denmark. MDM Policy Pract. 2023;8(1):23814683231159023. (Hvidberg et al. 2023)	EQ-5D-3L, for the disutility of myocardial infarction, stroke, and heart failure	Desk research	Section 10.4.4

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
Cooper JT, Lloyd A, Sanchez JJG, Sörstadius E, Briggs A, McFarlane P. Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. Health Qual Life Outcomes. 2020 Sep 21;18(1):310. doi: 10.1186/s12955-020-01559-x. (Cooper et al. 2020)	CKD Stage 3/4/5 utilities Haemodialysis, peritoneal dialysis, and transplant/post-transplant utilities	Desk research	Section 10.4
Andersson C, Hansen D, Sørensen SS, McGrath M, McCausland FR, Torp-Pedersen C, Schou M, Køber L, Pfeffer MA. Long-term cardiovascular events, graft failure, and mortality in kidney transplant recipients. Eur J Intern Med. 2024 Mar;121:109-113. doi: 10.1016/j.ejim.2023.10.026. Epub 2023 Oct 29. PMID: 37903704. (Andersson et al. 2024)	Successful transplant probability	Desk research	Section 9.3.4
Pruett, T. L., Vece, G. R., Carrico, R. J. & Klassen, D. K. 2021. US deceased kidney transplantation: Estimated GFR, donor age and KDPI association with graft survival. EClinicalMedicine, 37, 100980. (Pruett et al. 2021)	Post-transplant distribution	Desk research	Sections 9.3 and 9.3.4
Davies S. The future of peritoneal dialysis. Clin Kidney J. 2024 Nov 22;17(Suppl 2):9-18. doi:	Shares on haemodialysis and peritoneal dialysis	Desk research	Section 10.4.4

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
10.1093/ckj/sfae277. PMID: 39583141; PMCID: PMC11581766. (Davies 2024)			
Quist SW, van Loon J, Bakker S, Pochopién M, Postma MJ, Paulissen J. Cost-effectiveness of treatment with finerenone in mild to advanced stage chronic kidney disease patients with type 2 diabetes from a societal perspective. BMJ Public Health. 2025 Jun 25;3(1):e001288. doi: 10.1136/bmjph-2024-001288. PMID: 40575069; PMCID: PMC12198875. (Quist et al. 2025)	Impact of CKD on mortality	Desk research	Section 8.1
Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3(7):514-25. (Matsushita et al. 2015)	Impact of CKD on the risk of health events	Desk research	Section 8.1
Bellanca, L., Linden, S. & Farmer, R. 2023. Incidence and prevalence of heart failure in England: a descriptive analysis of linked primary and secondary care data - the PULSE study. BMC Cardiovasc Disord, 23, 374. (Bellanca et al. 2023)	General population heart failure prevalence	Desk research	Section 8.1

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
Korsgaard S, Christiansen CF, Pedersen L, Sørensen HT, Schmidt M. Breaking Point Toward Decreasing Prevalence of Myocardial Infarction Owing to Relative Stronger Decrease in Incidence Than Increase in Survival Rate (A Danish Cohort Study [1994-2016]). Am J Cardiol. 2021 Dec 1;160:8-13. doi: 10.1016/j.amjcard.2021.08.032. Epub 2021 Sep 27. PMID: 34593217. (Korsgaard et al. 2021)	General population myocardial infarction prevalence	Desk research	Section 8.1
Torkilseng EB, Clarke N, Sopina L, Oddershede L, Wolf RT, Lawrance R, Trigg A, Bennett B, Shaw JW. Predicting Danish EQ-5D-5L Utilities Based on United Kingdom EQ-5D-3L Utilities for Use in Health Economic Models. Pharmacoecon Open. 2025 May;9(3):433-443. doi: 10.1007/s41669-025-00562-6. Epub 2025 Feb 22. (Torkilseng et al. 2025)	Mapping from EQ-5D-3L UK tariff to EQ-5D-5L DK tariff	Desk research	Section 10.4.4; Appendix G.3

6. Clinical Studies

A systematic literature review (SLR) detailed in Appendix H was conducted to ensure an exhaustive review of relevant literature and increase understanding of the treatment landscape for C3G and IC-MPGN. The present application is based on the pivotal Phase III clinical trial for the efficacy and safety of pegcetacoplan, VALIANT, which compared the addition of pegcetacoplan to a placebo (Fakhouri et al. 2025b).

6.1 Efficacy of pegcetacoplan Compared to Placebo for Patients with C3G or Primary IC-MPGN

6.1.1 Relevant Studies

The VALIANT study was a phase 3, randomised, placebo-controlled, double-blinded, multicentre study and designed to assess the efficacy and safety of pegcetacoplan in patients with C3G or IC-MPGN. The influence of pegcetacoplan on quality of life was also assessed (Fakhouri et al. 2025b). The study design (Figure 13), study duration and PICO criteria are summarised in Table 15.

Further information is available in Appendix A and Appendix B.

In this trial, patients participated in a 26-weeks randomised controlled period (RCP), receiving either pegcetacoplan or placebo. Thereafter, patients entered a open-label period (OLP) in which patients previously receiving pegcetacoplan entered the pegcetacoplan-to-pegcetacoplan arm and patients previously receiving placebo the placebo-to-pegcetacoplan arm. Including the OLP, 10 (8.1%) patients discontinued study treatment. In the pegcetacoplan-to-pegcetacoplan arm, four (6.3%) patients discontinued due to adverse events (AEs). [redacted] ([redacted]%) participants in the pegcetacoplan-to-pegcetacoplan arm withdrew from the study due to [redacted] or [redacted] decision and [redacted] ([redacted]%) due to [redacted]. In the placebo-to-pegcetacoplan arm, [redacted] ([redacted]%) patients discontinued because of AEs, [redacted] ([redacted]%) withdrew consent, [redacted] ([redacted]%) became pregnant, and [redacted] ([redacted]%) discontinued due to [redacted]. Moreover, [redacted] ([redacted]%) participant was lost to follow-up, [redacted] ([redacted]%) withdrew consent, [redacted] ([redacted]%) withdrew due to investigator or medical monitor decision, and [redacted] ([redacted]%) due to pregnancy (Sobi 2025c).

The internal validity of the VALIANT trial is supported by its randomised, double-blind, placebo-controlled design, which helps minimise selection, performance, and measurement bias. The use of objective, pre-specified endpoints such as proteinuria reduction, eGFR change, and histologic assessment of complement deposition provides reliable and quantifiable measures of treatment effect in patients with C3G and primary IC-MPGN. The external validity of the VALIANT trial is supported by the inclusion of both adolescent and adult patients and the enrolment of individuals with native kidney disease as well as post-transplant disease manifestations. The multinational, multicentre study design enhances the representativeness of the study population relative to real-world clinical settings.

Table 15. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
Phase III Study Assessing the Efficacy and Safety of Pegcetacoplan in Patients With C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis (VALIANT) NCT05067127 (Fakhouri et al. 2025b)	Randomised, placebo-controlled, double-blinded, multicentre, Phase III study of pegcetacoplan versus placebo.	10 weeks screening period, 26 weeks double-blinded period followed by 26 weeks open-label, and 8 weeks follow-up (70 weeks in total). Patients that were randomised to placebo switched to open-label pegcetacoplan after Week 26.	Patients with C3G or primary IC-MPGN	Pegcetacoplan (subcutaneous administration), 1080 mg for adults or adolescents >50 kg and weight-based dosing for adolescents <50 kg twice weekly in addition to any pre-existing standard of care.	Subcutaneous placebo twice weekly in addition to any pre-existing standard of care	Change from baseline in log-transformed uPCR (Week 26 and 52), percentage of subjects who achieved the composite renal endpoint (Week 26 and 52), percentage of subjects with a reduction of at least 50% from baseline in uPCR (Week 26 and 52), change from baseline in C3G histologic index activity score (Week 26), percentage of subjects who showed decrease in C3c staining on renal biopsy from baseline (Week 26), change from baseline in eGFR (Week 26 and 52), proportion of patients achieving proteinuria <1 g/day (Week 24), percentage of subjects with normalisation of serum albumin levels (Week 26), percentage of subjects with serum C3 levels above lower limit of normal (Week 26), change from baseline in the functional assessment of Chronic Illness Therapy-Fatigue score (Week 26), change from baseline in the KDQoL score (Week 26)

Abbreviations: eGFR, estimated glomerular filtration rate; KDQoL, Kidney Disease Quality of Life; uPCR, Urine Protein-to-Creatinine Ratio

6.1.2 Comparability of Studies

Not relevant. The application is based on the head-to-head study VALIANT.

6.1.2.1 Comparability of Patients Across Studies

Not relevant. The application is based on the head-to-head study VALIANT.

Table 16. Patients' baseline characteristics in included studies used in the comparative analysis of effectiveness and safe ty

	[Study name]		[Study name]		[Study name]	
	[int ./ comp .]	[int ./ comp .]	[int./comp .]	[int ./ comp .]	[int ./ comp .]	[int./comp .]
Age						
Sex						

6.1.3 Comparability of Study Population(s) with Danish Patients Eligible for Treatment

The comparability between the study population and the Danish population are considered high as confirmed by a Nordic clinical expert (Sobi 2026). Therefore, values from the study population were used to inform the health economic model (Table 17).

Table 17. Characteristics of the relevant Danish population and input parameters in the health economic model

	Danish population (Sobi 2024a)	Study population	Health economic model (Sobi 2024a)
Age (years)	25.97	25.97	XXXX
Sex (% male)	43.55	43.55	XXXX
Body weight (kg)	63.09	63.09	XXXX

6.1.4 Analysis Method

Primary efficacy endpoint

The primary efficacy endpoint was the log-transformed ratio of uPCR at Week 26 compared to baseline. The null (H1,0) and alternative (H1,1) hypotheses for the primary efficacy analysis were:

$H_{1,0}$: There was 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 was a difference in log-transformed ratio of uPCR at Week 26 compared to baseline between the pegcetacoplan and placebo treatment groups.

uPCR values were expected to be highly skewed so that the values were natural log-transformed in analysis and presentation.

Baseline uPCR value was calculated as the average of the uPCR measurements from at least six of the nine first-morning spot urine (FMU) samples collected between the start of screening and Day 1, inclusive. The uPCR values used to calculate baseline included those from the samples collected on Day −2, Day −1, and before dosing on Day 1. In situations where less than six samples or more than nine samples were collected, the average of all collected samples was used for baseline derivation. For scheduled visits where three collections were expected for calculating averages, if there were missing collections, the average was based on those available collections; if there were more than three collections available (e.g., additional unscheduled collections), the selection of three collections to be used for average calculation followed data handling conventions as specified in Study APL2-C3G-310 SAP Version 2.0, Section 13.4.

A Mixed Models for Repeated Measures (MMRM) was used to analyse the primary endpoint. The model included fixed categorical effects for treatment group, visit, disease type (C3G vs IC-MPGN), baseline immunosuppressants use (yes vs no), stratification factors, and the visit-by-treatment group interactions, as well as the continuous, fixed covariate of baseline log-transformed uPCR. As the primary estimate, the difference between treatment groups using a composite contrast of equal-weighted average over weeks 24, 25, and 26 was estimated (refer to sample SAS code section for more details) with its 95% CI and corresponding p-value. In addition, the geometric means and geometric mean ratios relative to baseline were also presented after converting the log-transformed values back to the original unit.

Intercurrent events (ICEs) strategy and handling are listed in Table 18. Imputation for the nonmonotone missing pattern (i.e., arbitrary missing pattern) was performed prior to the multiple imputation for the monotone missing pattern (i.e., where a missing uPCR measurement at a visit for a participant implied that uPCR measurements at all subsequent visits for that participant were missing). The missing data were filled in 100 times to generate 100 complete data sets. The 100 complete data sets were analysed by using the MMRM approach described above. Results from the 100 complete data sets were combined for inference using Rubin's rule. The observed values for uPCR were summarised by treatment group and visit. Summaries presented the descriptive statistics for baseline, absolute values, change, and percentage change from baseline data by visit. The mean change from baseline in uPCR (±SE) was plotted over time-by-treatment group. All uPCR data were listed for the ITT set.

Key secondary analyses

The key secondary efficacy endpoint of the proportion of participants who met the criteria for achieving a composite renal endpoint at Week 26 was examined with the following null ($H_{2,0}$) and alternative ($H_{2,1}$) hypotheses:

$H_{2,0}$: There was no difference in proportion of participants who met the criteria for achieving a composite renal endpoint at Week 26 between the pegcetacoplan and placebo treatment groups.

$H_{2,1}$: There was a difference in proportion of participants who met the criteria for achieving a composite renal endpoint at Week 26 between the pegcetacoplan and placebo treatment groups.

A participant met the requirements of the composite renal endpoint if they satisfied:

- A stable or improved eGFR compared to baseline (≤15% reduction in eGFR), and
- A ≥50% reduction in uPCR compared to baseline.

For requirement (1), the eGFR status at Week 26 was calculated using the following steps:

- Baseline eGFR value was calculated using the last non-missing assessment prior to first dose.
- Week 26 eGFR value was calculated based on the Week 26 assessment result.
- Each participant was categorised as either a “stable or improved” or not “stable or improved” according to whether the change from baseline in eGFR calculated from steps 1 and 2 is a reduction of no more than 15%.

For requirement (2), the uPCR response status at Week 26 was calculated using the following steps:

- Baseline uPCR value was calculated as the average of the uPCR measurements from at least six of the nine 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 six of the nine FMU samples collected in Week 24, Week 25, and Week 26.
- Each participant was categorised as either a success or a failure according to whether the change from baseline in uPCR calculated from steps 1 and 2 was a reduction of at least 50%.

A logistic model was used to analyse the key secondary endpoint. The model included treatment group as the independent variable and adjusted for baseline eGFR values, baseline log-transformed uPCR values, disease type (C3G vs IC-MPGN), and stratification factors. A composite strategy was used for addressing the ICEs listed in Table 18. In the composite strategy, the composite renal endpoint status at or after the occurrence of any of these ICEs was regarded as nonresponder. Additionally, participants with missing eGFR and/or uPCR values at Week 26 for reasons other than those listed as ICEs were

regarded as nonresponders. The numbers and proportion of participants who met the criteria for achieving a composite renal endpoint at Week 26 were tabulated by treatment group, including detailed breakdown on each of the two requirements. All composite renal endpoint achievement data were listed for the ITT set.

Renal biopsy endpoints were only evaluated for adult patients and were not required for participants younger than 18 years of age. Therefore, ''Change in the activity score of the C3G histologic index score from baseline'' and '' Proportion of participants showing decreases in C3c staining on renal biopsy from baseline'' were evaluated only for adults.

Table 18. Estimands and attributes for primary, key secondary, and additional secondary endpoints

Estimands and attributes for primary, key secondary, and additional secondary endpoints		
For all estimands: Population: participants with C3G or IC-MPGN defined through the study inclusion/exclusion criteria in the ITT set Treatment regimens of interest: • Twice-weekly SC doses of pegcetacoplan for up to 52 weeks of treatment • Twice-weekly SC doses of placebo for up to 26 weeks of treatment		
C: Variable (or endpoint)	D: Strategies for addressing ICEs (event†: strategy‡)	E: Population-level summary
Primary Estimand		
Log-transformed ratio of uPCR at Week 26 compared to baseline	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change of log-transformed uPCR from baseline to Week 26 (measured by equal-weighted average over weeks 24, 25, and 26) between the pegcetacoplan group and the placebo group.
Key Secondary Estimands (for comparative endpoints)		
The proportion of participants who meet the criteria for achieving a composite renal endpoint at Week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving a composite renal endpoint for the pegcetacoplan group to achieving a composite renal endpoint for the placebo group at Week 26.
The proportion of participants with a reduction of at least	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving a reduction of at least 50% from baseline in uPCR for the pegcetacoplan group to

50% from baseline in uPCR at Week 26		achieving a reduction of at least 50% from baseline in uPCR for the placebo group at week 26.
For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index score at week 26	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change from baseline to Week 26 in activity score between the pegcetacoplan group and the placebo group.
The proportion of participants with evaluable renal biopsies showing decreases in C3c staining on renal biopsy from baseline at Week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of showing decreases in C3c staining for the pegcetacoplan group to showing decreases in C3c staining for the placebo group at Week 26.
Change from baseline in eGFR at Week 26	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change of eGFR from baseline to Week 26 between the pegcetacoplan group and the placebo group.

†ICE definitions: ProhibiRescue = use of prohibited concomitant medication specified in Study APL2 C3G-310 Protocol, Section 8.3.3, or use of rescue therapies defined in Study APL2 C3G-310 Protocol, Section 8.3.2; RenalReplace = start renal replacement therapy (dialysis and/or renal transplant);DisctTrt = permanent discontinuation of study treatment

‡Strategies: Composite strategy: the endpoint status at or after the initiation of the ICEs will be regarded as non-responder; Hypothetical strategy: (for ICEs due to ProhibiRescue) all measurements after the ICEs will be set to missing. Missing data resulting from the ICEs will be imputed using copy reference imputation. (for ICEs due to RenalReplace) all measurements after the ICEs will be set to missing. Missing data resulting from the ICEs will be imputed based on the worst change of all participants across visits plus a random error; Treatment policy strategy: all measurements after the ICEs will be used as is. Missing data resulting from the ICEs will be imputed using copy reference imputation.

Abbreviations: C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; ICE, intercurrent event; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; ITT, intention-to-treat; SC, subcutaneous; uPCR, urine protein creatinine ratio

Source: (Sobi 2024b)

Missing values were only collected for eGFR- and uPCR-related outcomes, i.e. missing eGFR and uPCR measurements were collected. All patients had baseline values for eGFR and uPCR. A value was considered missing when there was a value at a later timepoint for a specific patient. If the last collected value was before the end of the study, following missing values were not considered. Missing inputations were made using Last Observation Carried Forward. In total, there were 35 data points for which inputations of eGFR were made and 53 for which inputations of uPCR were made.

6.1.5 Effect – Results per Study [VALIANT]

A summary of outcomes from the VALIANT trial is shown in Table 19.

Table 19. Summary of outcomes from the VALIANT trial

Outcome	Chosen population	Pegcetacoplan (N=63)	Placebo (to pegcetacoplan for Week 52) (N=61)	Diff (95% CI) vs placebo	p-value
Change from baseline in log-transformed uPCR, LS mean (SE; 95% CI) and % change from baseline (below dotted line) (Week 26 [top] and 52 [bottom])	ITT	[redacted]	[redacted]	[redacted]	[redacted]
		-67.2 (-74.9, -57.2)	2.9 (-8.6, 15.9)	68.1 (57.3, 76.2)	<0.001
		[redacted]	[redacted]	[redacted]	NR
Proportion of participants achieving the composite renal endpoint, n (%)* (Week 26 [top] and 52 [bottom])	ITT	31 (49.21)	2 (3.28)	[redacted]	[redacted]
		[redacted]	[redacted]	NR	NR
Proportion of participants with ≥50% reduction in uPCR, n (%) (Week 26 [top] and 52 [bottom])	ITT	38 (60.32)	3 (4.92)	[redacted]	[redacted]
		[redacted]	[redacted]	NR	NR

Change in the activity score of the C3G histologic index score from baseline, LS mean (95% CI) (Week 26)	ITT, adults only (pegcetacoplan N=35, placebo N=34)	−3.482 (−4.721, −2.244)	−2.480 (−3.775, −1.186)	−1.002 (−2.803, 0.798)	p=0.2753
Proportion of participants showing decreases in C3c staining on renal biopsy from baseline, n (%) (Week 26)	ITT, adults only (pegcetacoplan N=35, placebo N=34)	26 (74.29)	4 (11.76)	[redacted]: [redacted] ([redacted], [redacted])	[redacted]
Change in eGFR from baseline, LS mean (95% CI) (Week 26 [top] and 52 [bottom])	ITT	−1.497 (−5.892, 2.899)	−7.808 (−11.570, −4.047)	6.312 (0.501, 12.122)	Nominal p=0.0333
		[redacted] ([redacted]; [redacted], [redacted])	[redacted] ([redacted]; [redacted], [redacted])	[redacted] ([redacted] to [redacted])	NR

* 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 six of the 9 FMU samples collected between the start of screening and Day 1, inclusive. Week 26/52 eGFR value was calculated based on the Week 26/52 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, or Week 52, respectively. Participants who met criteria for achieving a composite renal endpoint were defined as: (1) a stable or improved eGFR compared to baseline (≤15% reduction in eGFR), and (2) a ≥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 nonresponder. Participants with missing eGFR and/or uPCR values at Week 26/52 for reasons other than ICEs were regarded as nonresponder.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ICE, intercurrent event; ITT, intention-to-treat; LS, least square; NR, not reported; OR, odds ratio; uPCR, urine protein creatinine ratio

Source: (Fakhouri et al. 2025b, Sobi 2024a, Sobi 2025c)

6.1.6 Effect – Results per [Study name 2]

Not applicable.

7. Comparative Analyses

7.1 Analysis Method

Not applicable for this submission.

7.2 Results of the Comparative Analysis

Table 20 displays the results from the comparative analysis of the head-to-head VALIANT trial.

Table 20. Results from the comparative analysis of pegcetacoplan vs placebo in patients with C3G or I-MPGN at Week 26

Outcome measure	Pegcetacoplan (N=63)	Placebo (N=61)	Result
Change from baseline in log-transformed uPCR, LS mean (SE; 95% CI)	[redacted]	[redacted]	[redacted]
Proportion of participants achieving the composite renal endpoint, n (%)	31 (49.21)	2 (3.28)	[redacted]
Proportion of participants with ≥50% reduction in uPCR, n (%)	38 (60.32)	3 (4.92)	[redacted]
Change in the activity score of the C3G histologic index score from baseline, LS mean (95% CI)	−3.482 (−4.721, −2.244)	−2.480 (−3.775, −1.186)	−1.002 (−2.803, 0.798), p=0.2753
Proportion of participants showing decreases in C3c staining on renal biopsy from baseline, n (%)	26 (74.29)	4 (11.76)	[redacted]
Change in eGFR from baseline, LS mean (95% CI)	−1.497 (−5.892, 2.899)	−7.808 (−11.570, −4.047)	6.312 (0.501, 12.122), [redacted]
Proportion of participants achieving	[redacted]	[redacted]	[redacted]

proteinuria <1 g/day, proportion (SE; 95% CI)			
Proportion of participants achieving normalisation of serum albumin levels, proportion (SE; 95% CI)	[redacted]	[redacted]	[redacted]
Proportion of participants with baseline serum C3 levels below the LLN who achieve serum C3 levels above the LLN, proportion (SE; 95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: C3G, C3 Glomerulopathy; eGFR, estimated glomerular filtration rate; LLN, lower limit of normal; LS, least square; SE, standard error; uPCR, urine protein creatinine ratio

Source: (Sobi 2024a, Fakhouri et al. 2025b)

7.3 Effect – Results per [Outcome]

Not applicable.

8. Safety

This section provides summarised safety information for the RCP of the VALIANT trial. The 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.

Serious adverse events (SAEs) and safety information regarding the OLP, as well as detailed safety information regarding the RCP, are detailed in Appendix F.

Table 21. Overview of adverse events during the RCP (Safety Set)

	Pegcetacoplan (N=63)	Placebo (N=61)	Difference, % points	Difference, RR (95% CI)
All adverse events (AE), n (%)	53 (84.1)	26 (42.6)	41.5	1.974 (1.447, 2.692)
Serious AE (SAE), n (%) [1]	6 (9.5)	6 (9.8)	-0.3	0.968 (0.330, 2.838)
AE grade ≥3, n (%) [2]	NR	NR	NR	NR
Dose reduction due to AE, n (%)	NR	NR	NR	NR

	Pegcetacoplan (N=63)	Placebo (N=61)	Difference, % points	Difference, RR (95% CI)
Treatment discontinuation due to AE, n (%)	[redacted]	1 (1.6)	[redacted]	[redacted]

1 See ICH definition. 2 CTCAE v. 5.0 is preferred

Abbreviations: AE = adverse event; CI, confidence interval; NR, not reported; RR, risk ratio; SAE, serious adverse event

Source: (Sobi 2024a)

The most commonly reported treatment-emergent adverse events (TEAEs) (≥10%) in either group (pegcetacoplan vs placebo) were pyrexia ([redacted]% vs [redacted]%), nasopharyngitis ([redacted]% vs [redacted]%), headache ([redacted]% vs [redacted]%) and vomiting ([redacted]% vs [redacted]%) (Table 22). [redacted] SAE had a frequency of ≥3%. A complete list of SAEs in provided in Appendix F.

Table 22. Proportion of patients with adverse events during the RCP (Safety Set)

	Pegcetacoplan (N = 63)		Placebo (N = 61)	
	All [1]	**Grade ≥3 or SAE [2]**	**All [1]**	**Grade ≥3 or SAE [2]**
Pyrexia, n (%)	[redacted]	NA	[redacted]	NA
Nasopharyngitis, n (%)	[redacted]	NA	[redacted]	NA
Headache, n (%)	[redacted]	NA	[redacted]	NA
Vomiting, n (%)	[redacted]	NA	[redacted]	NA

1 List all adverse events with a frequency of ≥10%. 2 Report SAEs if adverse events are not CTCAE graded and indicate events with a frequency of ≥3% in either arm.

Abbreviations: NA, not applicable; SAE, serious adverse event

Source: (Sobi 2024a)

8.1 Safety Data from External Literature applied in the Health Economic Model

The kidney filtration rate informs about its proper functionality and, as it was shown by Matsushita et al. (2015), large variations from normal eGFR level (~90 mL/min per 1.73 m^2) increases the risk of cardiovascular (CV) events, such as heart failure, stroke, coronary heart disease, and CV mortality. The events were considered cumulatively, i.e. after the initial cycle of the event, patients are considered to be post-event and the corresponding cost and disutility is applied. Patients can experience several events with

the same probability as the first event (i.e. there is no adjustment for recurrent events). The general population risk of the events used are presented in Table 23.

Table 23. Probabilities of health events per cycle

Age category	Stroke	Heart failure	CV mortality	Myocardial infarction
0-4	0.00002	0.00007	0.00000	0.00000
5-9	0.00002	0.00007	0.00000	0.00000
10-14	0.00002	0.00007	0.00000	0.00000
15-19	0.00002	0.00007	0.00000	0.00000
20-24	0.00002	0.00007	0.00000	0.00000
25-29	0.00002	0.00007	0.00000	0.00013
30-34	0.00002	0.00007	0.00001	0.00013
35-39	0.00002	0.00007	0.00001	0.00013
40-44	0.00012	0.00007	0.00003	0.00013
45-49	0.00012	0.00057	0.00006	0.00292
50-54	0.00024	0.00057	0.00009	0.00292
55-59	0.00024	0.00057	0.00017	0.00648
60-64	0.00045	0.00057	0.00032	0.00642
65-69	0.00045	0.00204	0.00061	0.01169
70-74	0.00091	0.00204	0.00094	0.01157
75-79	0.00091	0.00541	0.00166	0.02102
80-84	0.00160	0.00541	0.00324	0.02014
85-89	0.00160	0.01237	0.01468	0.02484
90-95	0.00274	0.01237	0.01468	0.02330
95-99	0.00274	0.01237	0.01468	0.02129
100-104	0.00274	0.01237	0.01468	0.02129

Abbreviations: CV, cardiovascular

References: (Public Health England 2018, Bellanca et al. 2023, Statistics Denmark 2026, Korsgaard et al. 2021)

For each type of CV event, hazard ratios (HR) within eGFR ranges are applied in the model (Table 24).

Table 24. Impact of CKD on the risk of health events

Health state	HR	Source
Stroke		
CKD1	1.13	Matsushita et al. (2015)
CKD2	1.00	
CKD3	1.11	
CKD4	1.52	
CKD5	1.52	
HD	1.52	
PD	1.52	
Heart failure		
CKD1	1.09	Matsushita et al. (2015)
CKD2	1.11	
CKD3	1.71	
CKD4	2.52	
CKD5	2.52	
HD	2.52	
PD	2.52	
CV mortality		
CKD1	1.32	Matsushita et al. (2015)
CKD2	1.10	
CKD3	1.58	
CKD4	2.62	
CKD5	2.62	

HD	2.62	
PD	2.62	
Myocardial infarction		
CKD1	1.00	Matsushita et al. (2015)
CKD2	1.00	
CKD3	1.73	
CKD4	2.23	
CKD5	2.23	
HD	2.23	
PD	2.23	

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HD, haemodialysis; PD, peritoneal dialysis

The general population mortality was sourced from the Danish Medicines Council model template. The increased mortality per health state is captured using HRs and were sourced from Quist et al. (2025) (Table 25).

Table 25. Impact of CKD on mortality

Health state	HR	Source
CKD1	1.14	Quist et al. (2025)
CKD2	1.14	
CKD3	1.33	
CKD4	6.42	
CKD5	9.49	
HD	10.04	
PD	10.04	
Transplant	2.50	

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

9. Extrapolation of patient transitions

9.1 Clinical Data Used for Extrapolation of Patient Transitions

Transition probabilities between uPCR health states were derived from a statistical analysis of patient-level data on uPCR from the VALIANT trial for both the intervention and comparator. Transition probabilities between CKD states were, for both the intervention and comparator, derived from the eGFR decline estimates by considering the baseline distribution of patients across CKD stages, the eGFR ranges defining each stage, and the corresponding rates of eGFR decline in VALIANT. In addition, stable disease probability was estimated based on the proportion of patients achieving stable disease at end of follow-up in VALIANT. The post-transplant uPCR distribution was derived from VALIANT as well. For transition probabilities where study data was not viable to use, alternative data sources were utilised. A summary of the methods and sources used to derive all the transition probabilities in the model is provided in Table 27. Detailed descriptions of the approaches used to derive the transition probabilities are provided in Sections 9.3.1, 9.3.2, 9.3.3 and 9.3.4.

9.2 Extrapolation Using Parametric Extrapolation Models

Not applicable.

9.2.1 Extrapolation of [Clinical Outcomes 1]

Not applicable.

Table 26. Overview of assumptions related to extrapolation of [clinical outcome]

Method/approach	Description/assumption
Data	
Selected distribution	
Models investigated	
Assumptions	
Proportional hazards between intervention and comparator	
Flexible parametric models	

Method/approach	Description/assumption
Cure point and/or share	
Treatment waning	
Any other assumptions	
Internal validity	
Distribution with best AIC fit	
Distribution with best BIC fit	
Distribution(s) with best visual fit on probability scale (e.g., Kaplan-Meier data)	
Distribution(s) with best visual fit according to evaluation of smoothed hazards	
External validity	
References for validating external validity	
Distribution with highest external validity	

9.2.2 Extrapolation of [Clinical Outcome 2]

Not applicable.

9.3 Extrapolation Using Transition Probabilities

The transition probabilities used in the health economic model are presented in Table 27. Where possible, data from the pivotal trial VALIANT were used. These have high validity, as they are based on randomised data with standardised outcome assessments. Observed differences between health states and treatment arms reflect expected treatment effects. Where not viable, local and disease-specific data were used to the greatest extent possible, reflecting the relevant healthcare setting and target population, ensuring clinically plausible and contextually relevant estimates.

Table 27. Transition probabilities in the health economic model

From health state	To health state	Transition probability, incl. calculation	Assumption	Reference
Any uPCR state	Any uPCR state	Transition probabilities for SoC only are presented in Table 31 and for pegcetacoplan in Table 32. The calculations to derive the transition probabilities are presented in section 9.3.1.	Not time-dependent. Different between arms, as described in section 9.3.1.	VALIANT (Sobi 2024a)
Any CKD state	Any CKD state	Transition probabilities were derived from eGFR decline estimates by considering the baseline distribution of patients across CKD stages, the eGFR ranges defining each stage, and the corresponding rates of eGFR decline. eGFR decline per uPCR range for pegcetacoplan and SoC only are presented in Table 34 and the derivation to transition probabilities in section 9.3.2.	Not time-dependent, but dependent on uPCR level. Different between arms, as described in section 9.3.2.	VALIANT (Sobi 2024a)
0.5 ≤ uPCR <1	Stable disease (uPCR<0.5 g/g)	Pegcetacoplan: XXXX% SoC only: XXXX% Derivation of transition	Not time-dependent. Different between arms, as described in section 9.3.3.	VALIANT (Sobi 2024a)

From health state	To health state	Transition probability, incl. calculation	Assumption	Reference
		probabilities is provided in section 9.3.3.		
Stable disease (uPCR<0.5 g/g)	0.5 ≤ uPCR <1	Pegcetacoplan and SoC only: XXXX% Derivation of transition probability is provided in section 9.3.3.	Not time-dependent. Not different between arms, as described in section 9.3.3.	Conservative estimate based on Caravaca-Fontan et al. (2020a)
CKD 5	Dialysis	Dialysis started after XXXXXXXXX (3 months) in CKD 5.	Not time-dependent. Not different between arms.	Assumption
Dialysis	Transplantation	Pegcetacoplan and SoC only: XXXX% Based on the median waiting time for a kidney (deceased donor) of XXX months reported in the Danish Nephrology Registry Red Report of 2023. This median time (T) was then converted into a per-cycle transition probability (P) using the following formula: [redacted]	Not time-dependent. Not different between arms.	Calculated based on Danish Nephrology Registry Red Report of 2023 (DNR 2023)
Transplantation	Any uPCR state	It is assumed that patients move back to the VALIANT baseline	Not time-dependent. Not different between arms.	VALIANT (Sobi 2024a)

From health state	To health state	Transition probability, incl. calculation	Assumption	Reference
		distribution (section 9.3.4)		
Transplantation	Any CKD state	Based on Pruett et al. (2021)	Not time-dependent. Not different between arms.	(Pruett et al. 2021)

Abbreviations: CKD, chronic kidney disease; uPCR, urine Protein-to-Creatinine Ratio

Due to the model including 23 health states, Table 28 is not viable to populate. Hence, the health economic model included in the application is referred to.

Table 28. Transition matrix for [intervention/comparator]

Off/On	State A	State B	State C	…

9.3.1 uPCR Health States

Transition probabilities between uPCR levels were derived from a statistical analysis of patient-level data from the VALIANT trial. 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. 3 months) and other covariates, including: treatment variable (pegcetacoplan, no pegcetacoplan), patients' age, and patients' sex. As patients in the "no pegcetacoplan" treatment arm were moved to the "pegcetacoplan" arm after 26 weeks of trial, data for those were removed from regression. Both ordered logistic regression models and multinomial logit models were tested and AIC values for all models are presented in Table 29.

Table 29. AIC values for the transition probability models

Model	AIC
Multinomial (AGE, SEX, ARM, HS)	[redacted]
Multinomial (AGE, ARM, HS)	[redacted]
Multinomial (SEX, ARM, HS)	[redacted]
Multinomial (ARM, HS)	[redacted]
Ordered logistic (AGE, SEX, ARM, HS)	[redacted]
Ordered logistic (AGE, ARM, HS)	[redacted]

Ordered logistic (SEX, ARM, HS)	XXXXXXX
Ordered logistic (ARM, HS)	XXXXXXX

Abbreviations: AIC, Akaike Information Criterion; AGE, patients' age; SEX, patients' sex; ARM, treatment arm; HS, health state

The multinomial logistic regression using only parameters for treatment arm and health state at previous visit was considered the most fitting based on AIC. Parameters estimates of the chosen regression model are presented in Table 30.

Table 30. Regression parameters of chosen transition probability model

Variable	To uPCR 1.0-3.0	To uPCR >3.0
Intercept	XXXX [XXXX, XXXX]	XXXXXX [XXXXXX, XXXXXX]
From uPCR 1.0-3.0	XXXX [XXXX, XXXX]	XXXXX [XXXXXX, XXXXXX]
From uPCR >3.0	XXXX [XXXX, XXXX]	XXXXX [XXXXXX, XXXXXX]
Placebo arm	XXXX [XXXX, XXXX]	XXXX [XXXX, XXXX]

Abbreviations: uPCR, urine protein-to-creatinine ratio

The derivation of transition probabilities between uPCR health states from the multinomial logistic regression model results is presented in Appendix E.2.3. In addition, the transition probabilities for SoC are only presented in Table 31 while the transition probabilities for pegcetacoplan are shown in Table 32.

Table 31. uPCR transitions SoC

From\To	uPCR <1.0	uPCR 1.0 - 3.0	uPCR >3
uPCR <1.0	XXXX%	XXXX%	XXX%
uPCR 1.0 - 3.0	XXXX%	XXXX%	XXXX%
uPCR >3	XXX%	XXXX%	XXXX%

Abbreviations: uPCR, urine protein-to-creatinine ratio

Table 32. uPCR transitions with pegcetacoplan

From\To	uPCR <1.0	uPCR 1.0 - 3.0	uPCR >3
uPCR <1.0	XXXX%	XXXX%	XXX%
uPCR 1.0 - 3.0	XXXX%	XXXX%	XXX%
uPCR >3	XXXX%	XXXX%	XXXX%

Abbreviations: uPCR, urine protein-to-creatinine ratio

9.3.2 CKD Health States

It has previously been shown that eGFR decline accelerates with increasing uPCR levels (Kashihara et al. 2026). To validate this relationship, an analysis was conducted using patient-level data from the VALIANT trial. 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. Additionally, patient's age and sex were tested as variables, but as they were not statistically significant, they were not included in finally chosen model. Model outcomes received from regression are presented in Table 33.

Table 33. eGFR decline linear regression analysis results

Variable	Estimate	P-value
Intercept	XXXX [XXXX, XXXX]	XXXX
Placebo arm	XXXX [XXXX, XXXX]	XXXX
uPCR 1.0 - 3.0	XXXX [XXXX, XXXX]	XXXX
uPCR >3	XXXX [XXXX, XXXX]	XXXX

Abbreviations: uPCR, urine protein-to-creatinine ratio

According to the results, patients with uPCR <1.0 treated with pegcetacoplan showed an increase in eGFR, indicating stabilisation of kidney function. However, extrapolating this eGFR improvement over the model time horizon was considered inappropriate. Therefore, a conservative assumption was made: no change in eGFR was applied for patients with uPCR <1.0 while on pegcetacoplan treatment. Consequently, this assumption was extended to all patients transitioning to stable disease, regardless of treatment arm. The eGFR decline inputs resulting from the regression are presented in Table 34.

Table 34. eGFR decline depending on uPCR level

Treatment / uPCR level	Pegcetacoplan	Standard of care
uPCR <1.0	X* [XXXX, X*]	XXXX [XXXX, X*]
uPCR 1.0 - 3.0	XXXX [XXXX, X*]	XXXX [XXXX, X*]
uPCR >3	XXXX [XXXX, X*]	XXXX [XXXX, X*]

* Conservatively no change in eGFR was assumed, regression result indicated the increase in eGFR of XXX

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

The eGFR decline estimates described above served as the basis for deriving transition probabilities between CKD stages in the model. Average time to CKD stage transition was calculated based on length of the eGFR ranges defining CKD stages (displayed in Table 35) and eGFR decline in uPCR stage (Table 34).

Table 35. Definition of CKD stages

CKD stage	Definition (eGFR values)	Length
CKD 1	≥90	XX*
CKD 2	60-89	XX
CKD 3	30-59	XX
CKD 4	15-29	XX
CKD 5	<15	XX

* Due to average eGFR in CKD 1 stage at baseline in VALIANT trial being XXXXX, it was assumed that CKD 1 will have length of XX

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

The average number of cycles to transition from CKD stage S to S+1 is:

[redacted]

Where Length S is the length of CKD stage S and Decline Z is the eGFR decline in uPCR stage Z. The transition probability from CKD stage S to S+1 is then calculated as:

[redacted]

9.3.3 Stable Disease Health State

Achieving stable disease has been suggested as a therapeutic goal in glomerulonephritis. Following Caravaca-Fontan et al. (2020a), stable disease in the model was defined using the criteria for normalisation of both eGFR and proteinuria. According to the study results on eGFR decline (see Section 9.3.2), all patients treated with pegcetacoplan who had a uPCR level below 1.0 g/g maintained stable eGFR. In the model, patients are additionally required to achieve a uPCR of less than 0.5 g/g in order to be considered as having stable disease. This requirement is broadly consistent with the definition of remission in clinical practice, as described by Caravaca-Fontan et al. (2020a).

Applying this definition to 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. The shares were X/XX (XX%) on SoC and XX/XX (XX%) in the pegcetacoplan arm. Due to the structure of the model calculations, the number of patients with stable disease had to be aligned with those who achieved uPCR <1.0 g/g, and this was converted into a per-cycle probability. The probability per cycle was calculated as the number of patients with uPCR <0.5 g/g divided by number of patients with uPCR <1.0 g/g (using data from week 52 for pegcetaoplan and week 26 for SoC only) and then adjusted for cycle length i.e.:

- For pegcetacoplan: [redacted]

- For SoC only: [redacted]

The results of this analysis are presented in the table below.

Table 36. Probability of disease stabilisation

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

Abbreviations: uPCR, urine protein-to-creatinine ratio; g/g, grams per gram; N, number of patients

References: (Sobi 2024a, Sobi 2025c)

The second model parameter defining disease stabilisation is its duration indicating the per cycle probability of relapse. In the model, the average time patients' disease is assumed to stay stable is [redacted]. A Nordic clinical expert stated that patients reaching a uPCR level of 0.5 g/g go into remission for a period of time ranging from weeks to life time (Sobi 2026). Caravaca-Fontan et al. (2020a) found that 33% of patients with C3G who had achieved remission with corticosteroids plus MMF and discontinued treatment experienced a relapse after a median time of 26 months (IQR, 15-79 months). This supports the plausibility of sustained stable disease in a substantial proportion. However, in contrast to Caravaca-Fontan et al. (2020a), patients remain on SoC and only pause pegcetacoplan treatment while in remission in the model, so an even longer time in stable disease could be expected. Hence, the [redacted] assumed is seen as conservative. This duration of stable disease was applied across both treatment arms, which is considered a conservative approach since it does not account for a potential extension of stable disease due to the strong disease-modifying effects of pegcetacoplan. For the purposes of the model calculations, the median time spent in the stable disease (T) state was converted into a per-cycle probability (P) using the following formula: [redacted]

Table 37. Duration of the stable disease / probability of disease relapse

Treatment	Median number of months of stable disease	Probability of relapse per cycle
Pegcetacoplan	[redacted]	[redacted]%
Standard of Care	[redacted]	[redacted]%

Reference: Caravaca-Fontan et al. (2020a)

In VALIANT, patients receiving pegcetacoplan with uPCR <1.0 g/g experienced, on average, an increase in eGFR, suggesting at least stabilisation of kidney function. In the model, only no eGFR worsening while patients remain in the stable state is assumed, which is seen as a conservative approach (Sobi 2024a, Sobi 2025c).

9.3.4 Transplant Health State

In the model, patients transition to kidney transplantation while in the dialysis health state, based on a per-cycle probability. This probability was derived from the Red Report from the Danish Nephrology Registry for 2023 (DNR 2023). According to these data, the median time for a kidney (deceased donor) is XXX months. This median time was converted into a per-cycle transition probability for use in the model of XXXX%. The same probability was assumed for both first and subsequent transplants.

Table 38. Probability of kidney transplantation from dialysis

Median number of months to receiving transplant	Probability of transplant per cycle
14.8	13.11%

Reference: (DNR 2023)

However, a proportion of patients will not be eligible for transplantation due to multimorbidity (Sobi 2025b). In the model, XX% of patients on dialysis are assumed to not be eligible for transplantation due to multiple chronic conditions. Furthermore, multimorbidity is assumed to increase with age. Therefore, patients aged 75 years or older are not considered eligible for transplantation in the model. Based on Andersson et al. (2024), a 97.8% probability of a successful transplant was assumed and applied in the first cycle following transplantation. Pruett et al. (2021) provided estimates for the post-transplant distribution of patients across CKD stages (Table 39). Regarding uPCR levels after transplant, it was assumed that patients will move back to the baseline distribution sourced from trial data (Table 40).

Table 39. Post-transplant distribution of patients across CKD stages

Parameter	Value
CKD1	6.57%
CKD2	32.95%
CKD3	52.24%*
CKD4	8.23%
CKD5	0.00%

Abbreviations: CKD, chronic kidney disease

Reference: Pruett et al. (2021)

Note: *CKD3 was assumed to be the sum of shares in CKD3A and CKD3B in Pruett et al. (2021)

Table 40. Post-transplant distribution of patients across uPCR stages

Parameter	Value
<1.0	XXX%
1.0 - 3.0	XXXX%
>3.0	XXXX%

Abbreviations: uPCR, Urine Protein-to-Creatinine Ratio

Reference: (Sobi 2024a)

9.4 Summary and Validity of Extrapolated Patient Transitions

Table 41. Modelled means in years, undiscounted estimates, half-cycle corrected and adjusted for background mortality

	Pegcetacoplan	SoC only	Difference
Total life years	XXXX	XXXX	XXX
Life years in CKD1	XXXX	XXX	XXXX
Life years in CKD2	XXXX	XXX	XXX
Life years in CKD3	XXXX	XXXX	XXX
Life years in CKD4	XXX	XXX	XXX
Life years in CKD5	XXX	XXX	XXX
Life years in transplant	XXX	XXX	XXX
Life years in haemodialysis	XXX	XXX	XXX
Life years in peritoneal dialysis	XXX	XXX	XXX
Life years in uPCR<1	XXX	XXX	XXX
Life years in uPCR 1.0 - 3.0	XXX	XXXX	XXX
Life years in uPCR >3	XXX	XXX	XXX

	Pegcetacoplan	SoC only	Difference
Life years in remission	XXXX	XXX	XXXX
Duration of treatment	XXX	XXX	XXX

Figure 3 Markov trace CKD states - pegcetacoplan

Figure 4 Markov trace CKD states - standard of care only

Figure 5 Markov trace uPCR states - pegcetacoplan

Figure 6 Markov trace uPCR states - standard of care only

9.5 Other Assumptions regarding Efficacy in the Model

Denmark has identified limited access to kidneys for transplantation as a major health system challenge and has therefore invested substantial societal resources in increasing organ donation and transplant capacity. The national action plan Fælles om at give livet tilbage prioritises expanded access to kidney transplantation through regulatory reform,

organisational optimisation, and broader utilisation of both deceased and living donors, including participation in Nordic exchange programmes and implementation of donation after circulatory death (Sundhedsstyrelsen 2025a; Dansk Center for Organdonation 2025a; Lex.dk 2025a; Lex.dk 2025b). These efforts are continuously monitored with respect to waiting lists and transplant outcomes (Dansk Center for Organdonation 2025b). Within this context, treatments that preserve kidney function and delay progression to end-stage kidney disease are expected to increase the availability of transplantable kidneys and improve access to transplantation. This constitutes a relevant system-level benefit aligned with Danish health policy priorities. Accordingly, the model considers increased access to kidney transplantation as a downstream consequence of Aspaveli's efficacy, as further detailed in this section.

9.5.1 Value of Saved Kidneys

A further long-term benefit of pegcetacoplan is the reduced demand for kidney transplants. The model incorporates this effect through the concept of opportunity cost: kidneys that would have been used for patients with C3G/IC-MPGN on SoC only, become available to other patients on the transplant waiting list due to treatment with pegcetacoplan leading to delaying or not requiring transplantation. This redistribution yields additional cost savings and QALY gains, in the analysis defined as the incremental savings and QALY gains resulting from patients receiving a transplant instead of remaining on dialysis, underscoring the broader health system value of the treatment. A Nordic clinical expert confirmed that reducing the need for transplantation through improved treatment of C3G and IC-MPGN would shorten waiting times for other patients in need of transplantation (Sobi 2026), making it reasonable to capture outcomes reflecting differences in costs and quality of life between dialysis and transplantation.

It should be understood that the full benefit of a saved kidney 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, i.e. 14.8 months (Section 9.3.4). 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. In the health economic analysis, a lifetime horizon is used. However, it is assumed that the total cumulative gains will occur only during the graft survival of each saved kidney, in the Nordics corresponding to 13.15 years (Figure 7.)(Scandia Transplant 2025). That the gains are restricted to the lifetime of a kidney can be seen as a conservative approach. Note that the distribution of gains between patients are not considered in the estimation, only that the total gains accrue over the average lifetime of a kidney.

In the model, the number of QALYs gained per additional kidney becoming available to other patients due to pegcetacoplan's kidney-sparing effect is estimated as:

[redacted]

Where $U_{transplant,}U_{HD}$ and U_{PD} is the utility per year in the transplanted state, on haemodialysis and peritoneal respectively (XXX, XXX and XXX, see Section 10), $Share_{HD}$

and $Share_{PD}$ are the shares on haemodialysis and peritoneal dialysis respectively ([redacted]% and [redacted]%, Section 10.4), and GS is graft survival, i.e [redacted]. Hence, $QALYs =$ [redacted].

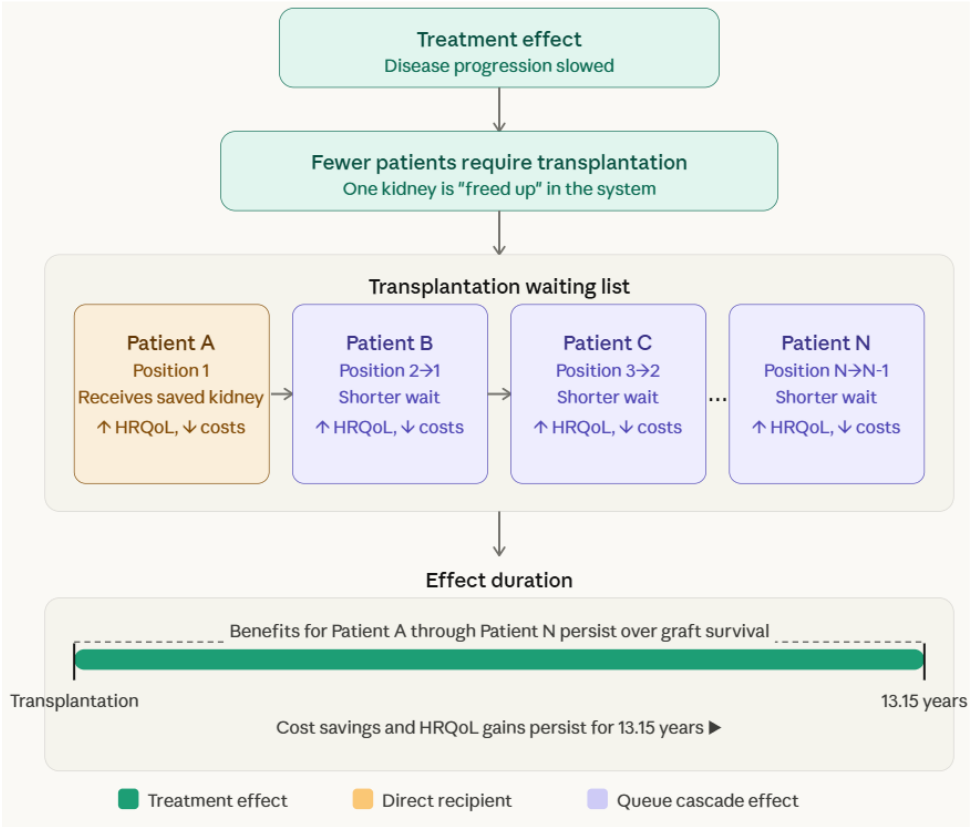
The corresponding cost saving is estimated as:

[redacted]

$Cost_{HD}$ and $Cost_{PD}$(i.e. the cost per year of haemodialysis and peritoneal dialysis) are [redacted] DKK and [redacted] DKK respectively (Section 11.2.2.2) and $Cost_{transplant}$ (i.e. the total cost of transplantation including post-transplant costs, see Section 11.2.2.3) is [redacted] DKK. Hence, $CostSaving =$ [redacted] DKK.

The total QALYs and cost savings in the model is then the QALY gain and cost saving per additional kidney becoming available multiplied by the number of saved kidneys per patient from using pegcetacoplan compared to SoC only. The average number of kidney transplants in the health economic model in the SoC only arm is [redacted]. The corresponding for patients on pegcetacoplan is [redacted]. Hence, the number of saved kidneys per patient amounts to [redacted]. In the model, the cost and QALY gain of saved kidneys occur at the time of transplant. The discounted cost gain from saved kidneys used in the base case amount to [redacted] DKK. The corresponding total QALY gain is [redacted] QALYs (Section 12).

Figure 7. Illustration of saved kidneys



Abbreviations: HRQoL: health-related quality of life

Note: Pegcetacoplan treatment leads to slowed disease progression compared to treatment with SoC only. Consequently, kidney transplantations for patients on pegcetacoplan are delayed or not required. This, in turn, leads to additionally available kidneys to other patients on the transplant waiting list. Illustrated is the effect of one additional kidney available for transplantation. Since Patient A receives a kidney, Patient B's waiting time for a kidney shortens, due to him moving from second in the transplant queue to 1st. Consequenctly, Patient C moves from third in line to second and Patient N from place N to N-1. In other words, the full benefit of a saved kidney is not realised by a single patient, instead, this reduction in dialysis time is effectively transferred to the next 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 benefits from the time saved due to a single additional kidney becoming available. Therefore, the total cumulative savings occur during the complete graft survival of each saved kidney, in the Nordics corresponding to 13.15 years (Scandia Transplant 2025).

A similar evaluation of the health and economic outcomes of kidney transplantation compared to dialysis is performed by Axelrod et al. (2018). A key result of the study is the estimated incremental QALY gain of up to 2.31 QALY 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 ESKD.

Solving the unmet need continues to be a priority in Denmark. Examples of investments include the implemented national strategy to strengthen organ donation and transplantation, with targets through 2029 to reduce waiting-list mortality, increase donor registration, and expand access to transplantation (Sundhedsstyrelsen 2025a). A central reform that is the opt-out consent model introduced on 1 June 2025, whereby adults are automatically included in the national donor register (Sundhedsstyrelsen 2025b). The Danish Centre for Organ Donation that coordinates nationwide clinical and organisational efforts, including hospital processes, professional training, and monitoring of outcomes (Dansk Center for Organdonation 2025a, Dansk Center for Organdonation 2025b). Donor pool through living donor exchanges via the Nordic Kidney Exchange Programme (STEP) and the use of donation after circulatory death (DCD) (Lex.dk 2025a, Lex.dk 2025b).

10. Health-Related Quality of Life

10.1 Overview

The EuroQol 5-dimension, 5-level QoL (EQ-5D-5L) and the EuroQol Visual Analogue Scale (EQ-VAS) questionnaires were used to evaluate the effects of pegcetacoplan (vs placebo) on the HRQoL of patients participating in VALIANT (Fakhouri et al. 2025b). However, the VALIANT trial included few patients in CKD stage 3 and 4 and none in CKD stage 5 or on dialysis. Therefore, based on available literature, utility values associated with CKD stages 3-5, dialysis, and transplant in the model were sourced from Cooper et al. (2020), to complement the utilities for CKD stages 1 and 2 sourced from VALIANT. Cooper et al. (2020), which was identified through desk research, examined various utility estimates related to CKD, including data reflecting the nationalities of patients, and provided UK-specific information on utility values associated with different CKD stages, dialysis, and transplantation. Cooper et al. (2020) and the derived utility inputs are described in Section 10.4.

Table 42. Overview of included instruments for measuring health-related quality of life

Instrument	Median follow-up time and data cut	Application	Source	Reference to description
EQ-5D	The last HRQoL assessment was made at Week 52 (12 February 2025)	Utility values for CKD1 and 2 Estimation of utility decrement for patients with elevated uPCR levels	VALIANT	Section 10.2.1

Abbreviations: EQ-5D, EuroQol 5-Dimension; CKD, Chronic Kidney Disease

Table 43. Basis for estimating utility values

Instrument	Preference weights	Source	Short description
EQ-5D-5L	DK	VALIANT	Section 10.2.1
EQ-5D-5L	DK	Cooper et al. (2020)	Utility values associated with CKD stages 3-5 in the model were sourced from Cooper et al. (2020), to complement the utilities for CKD stages 1 and 2 sourced from VALIANT (Section 10.4). Mapped from EQ-5D-3L UK tariff to EQ-5D-5L DK tariff using Torkilseng et al. (2025)
EQ-5D-3L	DK	(Hvidberg et al. 2023)	Disutility for myocardial infarction, stroke, and heart failure

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; EQ-5D-(3/5L), EuroQol 5-Dimension, (3/5-Level); SD, standard deviation; SEM; standard error of the mean; UK, United Kingdom

10.2 Instruments

10.2.1 EQ-5D

Below follows the HRQoL data from VALIANT using the EQ-5D instrument.

10.2.1.1 Study Design and Instrument

The ITT population contributing to HRQoL data in VALIANT was the same as that for other clinical outcome data. The study design of VALIANT is described in Section 6.1.1. The EQ-5D QoL data was captured during clinic visits. The EQ-5D is a validated, standardised questionnaire developed by the EuroQoL Group which is completed by patients to measure their overall health status. It is commonly used in clinical studies to provide a measure of patient utility for clinical and economic appraisals as it is a generic instrument used across various disease areas (EuroQol 1990). The EQ-5D-5L represents a revision to the original EQ-5D-3L (with three response levels per item) and has been shown to significantly increase reliability and sensitivity (discriminatory power) while maintaining ease of completion. The Danish tariff has been applied for this application.

10.2.1.2 Data Collection

An overview of the responses for the intervention and comparator is provided in Table 44, Table 45, and Table 46.

Table 44. Overview of responses for the intervention and the comparator

Time	Number of patients "at risk "* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk " at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Pegcetacoplan (N = 63)				
Baseline	XX	XX	XX%	XX %
Week 26	XX	XX	XX %	XX%
Week 52	XX	XX	XX%	XX%
Placebo (N = 61)				
Baseline	XX	XX	XX%	XX%
Week 26	XX	XX	XX%	XX%
Week 52	XX	XX	XX%	XX%

* Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted.

**Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t*/number of patients at randomisation.

Table 45. Overview of responses by health state - pegcetacoplan

Health state	Number of responses in health state N	Number of patients who have provided at least one response in the health state N
CKD1	[redacted]	[redacted]
CKD2	[redacted]	[redacted]
CKD3	[redacted]	[redacted]
CKD4	[redacted]	[redacted]
CKD5	[redacted]	[redacted]
uPCR <1 g/g	[redacted]	[redacted]
uPCR 1-3 g/g	[redacted]	[redacted]
uPCR >3 g/g	[redacted]	[redacted]

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

Table 46. Overview of responses by health state - placebo

Health state	Number of responses in health state N	Number of patients who have provided at least one response in the health state N
CKD1	[redacted]	[redacted]
CKD2	[redacted]	[redacted]
CKD3	[redacted]	[redacted]
CKD4	[redacted]	[redacted]
CKD5	[redacted]	[redacted]
uPCR <1 g/g	[redacted]	[redacted]
uPCR 1-3 g/g	[redacted]	[redacted]
uPCR >3 g/g	[redacted]	[redacted]

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

10.2.1.3 Results

EQ-5D-5L

A summary of the resulting EQ-5D-5L scores with Danish utility weights, at baseline, Week 26, and Week 52, are provided in Table 47.

The observed EQ-5D-5L index scores of patients in the pegcetacoplan arm remained [redacted] over time as visualised in Figure 8. It should be noted that patients in the comparator arm were switched from placebo-to-pegcetacoplan after 26 weeks in the VALIANT trial. Therefore, results for the comparator arm and treatment comparison at 52 weeks are not directly comparable.

Table 47. Results for EQ-5D-5L

Time	Intervention		Comparator		Difference
	N	Average (SE)	N	Average (SE)	Difference (95%CI)
Baseline	51	[redacted]	56	[redacted]	[redacted]
Week 26	42	[redacted]	41	[redacted]	[redacted]
Week 52	44	[redacted]	40	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5-Dimension, 5-Level; HRQoL, health-related quality of life; SE, standard error

Source: (Sobi 2024a, Sobi 2025c)

Figure 8. EQ-5D-5L values in time

Abbreviations: CI, Confidence interval; EQ-5D, EuroQoL Five-Dimension (Five-Level)
Source: (Sobi 2024a, Sobi 2025c)

EQ-VAS

A summary of the EQ-VAS scores with Danish utility weights, at baseline, Week 26 and Week 52, are provided in Table 48. As for the EQ-5D-5L index scores, the EQ-VAS results remained XXXXXX over time with XXXX confidence intervals as visualised in Figure 9.

Table 48. Results for EQ-VAS

Time	Intervention		Comparator		Difference
	N	Average (SE)	N	Average (SE)	Difference (95%CI)
Baseline	50	XXXX (XXXX)	55	XXXX (XXXX)	XXXX (95% CI: XXXX XXXX) p-value= XXXX
Week 26	43	XXXX (XXXX)	42	XXXX (XXXX)	XXXX (95% CI: XXXX , XXXX) p-value= XXXX
Week 52	44	XXXX (XXXX)	41	XXXX (XXXX)	XXXX (95% CI: XXXX , XXXX) p-value= XXXX

Abbreviations: CI, confidence interval; EQ-VAS, EuroQol Visual Analogue Scale; HRQoL, health-related quality of life; SE, standard error

Sources: (Sobi 2024a, Sobi 2025c)

Figure 9. EQ-VAS values in time

Abbreviations: CI: Confidence interval, EQ-VAS, EuroQol Visual Analogue Scale

Sources: (Sobi 2024a, Sobi 2025c)

When interpreting these results, it is important to recognise that clinical studies are often not powered to detect differences in HRQoL outcomes between treatment arms, as the sample sizes required would be disproportionately large relative to other clinical endpoints. Moreover, in the long-term, beyond what can be captured in a clinical study, the HRQoL gains associated with pegcetacoplan arise primarily from patients spending more time in less severe health states and less time in more severe states, particularly dialysis and transplantation, a pattern commonly observed when evaluating new treatments for progressive diseases.

10.2.2 ["Instrument 2"]

Not applicable.

10.2.2.1 Study Design and Instrument ["instrument 2"]

Not applicable.

10.2.2.2 Data Collection ["instrument 2"]

Not applicable.

10.2.2.3 Results ["instrument 2"]

Not applicable.

10.2.3 Summary when reporting multiple instruments

Not applicable.

10.3 Utility Values

Utility data from VALIANT used in the cost-effectiveness model include:

- Health state utility values for CKD 1 and CKD 2
- Disutility for elevated uPCR levels

10.3.1 Data Sources

Utility values were derived from EQ-5D data collected in the ITT population during clinic visits at baseline, Week 26 and Week 52. The ITT population contributing to HRQoL data in VALIANT was the same as that for other clinical outcome data. The study design of VALIANT is described in Section 6.1.1. Responses were converted to utility scores using the Danish value set. Age adjustment was performed in accordance with the Danish Medicines Council's methodological guidelines.

10.3.2 Calculation of Utility Values

In the VALIANT study, EQ-5D-5L questionnaires were collected and used to derive health state utilities through regression analysis of patient-level data. R software version 4.4.2 was used to perform analysis with the following process:

1. Responses to EQ-5D questionnaires were sourced VALIANT trial's patient data
2. Those responses were transformed to EQ-5D index values based on Danish tariff for EQ-5D-5L based on algorithm from Jensen et al. (2021) (using eq5d package for R)
3. Calculated EQ-5D Index parameter together with other explanatory parameters (patient's age and patient health state) are used in regression models to calculate impact of specific parameters on utility value
4. EQ-5D Index value on baseline (calculated in same way as mentioned in point 1 and 2) was used in linear regression model to account for patient's personal preferences when answering questionnaire
5. MMRM does not need EQ-5D baseline variable, as patient preference were taken into account by using random variable of subject ID in equation (as random variable it is not reported in result).
6. Utility value to be included in the model was calculated using the following [redacted] equation

[redacted]

Where [redacted] is the [redacted], [redacted] is the coefficient for [redacted] (added to account for correlation between observations for same individual), [redacted] is the coefficient for [redacted] (included to account for change in utility based on [redacted]), [redacted] is the coefficient for [redacted] and uPCR is a [redacted] variable assessing whether the patient's uPCR is higher than 1 g/g or not. No imputation of missing data was performed.

The results from the linear regression analysis are presented in Table 49.

Table 49. Utility linear regression analysis results

Variable	Estimate	P-value
Intercept	XXXX	XXXX
EQ-5D baseline value	XXXX	XXXX
Age	XXXX	XXXX
uPCR >1 g/g	XXXX	XXXX

Abbreviations: EQ-5D, EuroQoL Five-Dimension (Five-Level); uPCR, urine protein creatine ratio

Based on this result and the average EQ-5D of XXXX at baseline (Table 47), the final HSUV for CKD 1 and CKD 2 were calculated with the above XXXXXX regression equation resulted in a utility value of XXXX:

[redacted]

General population utility values for Denmark are sourced from the appendix to the Danish Medicines Council's methods guide (DMC 2021).

10.3.3 Adverse Events, Comorbidity and Other State-Specific Adjustments to Utility Values

The linear regression analysis mentioned in section 10.3.2 and presented in appendix G.4 suggests that a uPCR level greater than 1 g/g is associated with lower health state utility. Although this association was not statistically significant, achieving statistical significance in rare diseases can be challenging due to the relatively small sample sizes. Moreover, as mentioned in Section 10.2.1, lacking power in HRQoL outcomes is common in clinical trial data. However, the p-value is relatively close to 0.05, which may indicate a relationship that could not be confirmed with the available data. Based on this, an additional disutility of XXXX was applied in the model for patients with elevated uPCR levels (>1 g/g).

For patients in stable disease, the same utility as for patients with a uPCR level <1 g/g is assumed.

10.3.4 Results for Utility Values

An overview of the utility values based on VALIANT used in the health economic analysis is provided in Table 50.

Table 50. Utility values used in the health economic model

	Utility value [95% CI]	Instrument, preference weight	Source and reference
HSUVs			
CKD 1			
Stable disease	[redacted] [[redacted], [redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.2 and appendix G.4
uPCR <1.0 g/g	[redacted] [[redacted], [redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.2 and appendix G.4
uPCR 1.0-3.0 g/g	[redacted]* [[redacted], [redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.2, section 10.3.3 and appendix G.4
uPCR >3.0 g/g	[redacted]* [[redacted], [redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.2, section 10.3.3 and appendix G.4
CKD 2			
Stable disease	[redacted] [[redacted], [redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.2 and appendix G.4
uPCR <1.0 g/g	[redacted] [[redacted], [redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.2 and appendix G.4
uPCR 1.0-3.0 g/g	[redacted]* [[redacted], [redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.2, section 10.3.3 and appendix G.4
uPCR >3.0 g/g	[redacted]* [[redacted], [redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.2, section 10.3.3 and appendix G.4
Elevated uPCR decrement	[redacted] [[redacted]]	EQ-5D-5L, DK	VALIANT, section 10.3.3 and appendix G.4

* [redacted].

Abbreviations: CKD, chronic kidney disease; HSUV, health state utility value; uPCR, urine protein creatine ratio

References: (Sobi 2024a, Sobi 2025c)

10.4 Utility Values from External Sources

Utility data from other sources than VALIANT used in the cost-effectiveness model include: Health state utility values for CKD 3-5, transplant state and dialysis state and event disutilities.

Utility values associated with CKD stages 3-5 in the model were sourced from Cooper et al. (2020), to complement the utilities for CKD stages 1 and 2 sourced from VALIANT (Section 10.3). The disutility for patients with elevated uPCR levels was applied to the health state utilities sourced from Cooper et al. (2020) the same way as for the health state utilities derived from VALIANT data, described in Section 10.3.3. In addition, the health state utilities for the dialysis and transplant states were derived from Cooper et al. (2020). Utility values in Cooper et al. (2020) were collected using EQ-5D-3L and estimated using the UK tariff. These were mapped to Danish tariff EQ-5D-5L utilities using the algorithm described by Torkilseng et al. (2025). Further, disutilities were included for the events myocardial infarction, stroke, and heart failure.

10.4.1 Study Design

Cooper et al. (2020) conducted a SLR to identify HRQoL utility weights across different stages of CKD for use in economic evaluations. The authors searched MEDLINE and Embase (1999-2019) and included English-language studies with ≥25 participants that reported utility estimates related to CKD, including data reflecting the nationalities of patients, and provided UK-specific information on utility values associated with different CKD stages, dialysis, and transplantation. Interventional and observational studies were eligible. Studies were screened, graded for quality and relevance based on ISPOR Task Force criteria, and utility values were extracted and synthesised, including calculation of weighted means by CKD stage and treatment category.

10.4.2 Data Collection

Data were collected by systematically searching published literature, screening eligible studies, and extracting reported HRQoL utility values using a predefined data-extraction grid. No new patient-level data were collected.

10.4.3 Health-Related Quality of Life Results

Results in Cooper et al. (2020) were extracted from 17 studies graded as Grade 1 using the ISPOR Task Force criteria. Of these studies, 14 described more than one CKD health state utility (HSU) resulting in 58 CKD HRQoL estimates, providing utilities across multiple health states, among those CKD stages. In the review, ten studies (59%) utilised the EQ-5D-3L, four studies (24%) used the SF-6D, one study (6%) employed the Health Utilities Index Mark (HUI) 3, and two studies (12%) applied multiple instruments (HUI2 and HUI3; EQ-5D-3L and HUI3). Among the reported HSUVs, 18 (41%) pertained to dialysis patients, 17 (39%) to transplant patients, and 9 (21%) to cohorts categorised by CKD stage (Cooper et al. 2020).

10.4.4 HSUV and Disutility Results

Table 51 provides an overview of the utilities and disutilities sourced from the literature.

Table 51. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
CKD Stage 3	0.80 (95% CI: 0.69-1)	EQ-5D-3L	UK	Cooper et al. (2020)
CKD Stage 4	0.74 (95% CI: 0.62-0.85)	EQ-5D-3L	UK	Cooper et al. (2020)
CKD Stage 5	0.73 (95% CI: 0.62-1)	EQ-5D-3L	UK	Cooper et al. (2020)
Haemodialysis	0.44* (SD: 0.32)	EQ-5D-3L	UK	Cooper et al. (2020)
Peritoneal dialysis	0.53* (SD: 0.34)	EQ-5D-3L	UK	Cooper et al. (2020)
Transplant	0.71 (SD: 0.27)	EQ-5D-3L	UK	Cooper et al. (2020)
Disutilities				
Myocardial infarction	-0.00 [N/A]	EQ-5D-3L	DK	Table 4, ICD-10: I21-I22, Hvidberg et al. (2023) Disutility was calculated as the average of male and female.
Stroke	-0.01 [N/A]	EQ-5D-3L	DK	Table 4, ICD-10: I60, I61, I63-I64, Z501, Hvidberg et al. (2023) Disutility was calculated as the average of male and female.
Heart failure	-0.01 [N/A]	EQ-5D-3L	DK	Table 4, ICD-10: I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9, Hvidberg et al. (2023) Disutility was calculated as the average of male and female.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; EQ-5D-(3/5L), EuroQol 5-Dimension, (3/5-Level); SD, standard deviation; SEM; standard error of the mean; UK, United Kingdom

Note: * In the health economic model, 68.30% of patients on dialysis receive haemodialysis and 31.7% receive peritoneal dialysis (Davies 2024).

Sources: (Cooper et al. 2020, Hvidberg et al. 2023)

Table 52 provides an overview of the utilities and disutilities sourced from the literature, after adding the decrement from elevated uPCR levels (described in Section 10.3.3), as well as mapping the EQ-5D-3L values with the UK tariff to EQ-5D-5L (Appendix G.3).

Table 52. Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used[1]	Comments
CKD 3				
Stable disease	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	
uPCR <1.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	
uPCR 1.0-3.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	A decrement was applied for patients with elevated uPCR levels
uPCR >3.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	A decrement was applied for patients with elevated uPCR levels
CKD 4				
Stable disease	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	
uPCR <1.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	
uPCR 1.0-3.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	A decrement was applied for patients with elevated uPCR levels

uPCR >3.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	A decrement was applied for patients with elevated uPCR levels
CKD 5				
Stable disease	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	
uPCR <1.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	
uPCR 1.0-3.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	A decrement was applied for patients with elevated uPCR levels
uPCR >3.0 g/g	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	A decrement was applied for patients with elevated uPCR levels
Haemodialysis *	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	
Peritoneal Dialysis*	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	
Transplant	[redacted] [N/A]	EQ-5D-3L mapped to EQ-5D-5L	UK mapped to DK	

Note: * In the health economic model, 68.30% of patients on dialysis receive haemodialysis and 31.7% receive peritoneal dialysis (Davies 2024).

Values derived from the systematic literature depicted in Cooper et al. (2020) are based on multiple studies from and including different countries.

Abbreviations: CKD, chronic kidney disease; DK, Denmark; EQ-5D-3/5L, EuroQol 5-Dimension, 3/5-Level; SD, standard deviation; UK, United Kingdom; uPCR, urine protein creatine ratio

Source: (Sobi 2024a, Sobi 2025c, Cooper et al. 2020, Torkilseng et al. 2025)

11. Calculation of Costs

11.1 Drug Costs

11.1.1 Drug Costs for Intervention and Comparator

Patients on pegcetacoplan receive a dose of 1080 mg twice weekly. The pharmacy purchase price per package containing one vial is 25 704.75 DKK (Lægemiddelstyrelsen 2026c). Note that vial sharing is not viable. Also note that the price per vial is the same between the 1-vial package and the 8-vial package.

In addition, patients receiving pegcetacoplan receive it in combination with SoC, while patients in the comparator group receive SoC alone. The treatments included in the model as well as the doses used are presented in Table 53, while the drug costs as well as share of patients receiving each treatment included in SoC is presented in

Table 54.

Table 53. Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Pegcetacoplan	1080.00	100%	Twice weekly	NA
Ramipril	XXXX	100%	Daily	Yes
Losartan	XXXX	100%	Daily	Yes
Mycophenolate mofetil	XXXXXX	100%	Daily	Yes
Tacrolimus	XXX	100%	Daily	Yes
Mycophenolic acid	XXXXXX	100%	Daily	Yes
Azathioprine	XXXXX	100%	Daily	Yes
Prednisolone	XXXX	100%	Daily	Yes
Dapagliflozin	XXXX	100%	Daily	Yes

Table 54. Medicines used in the model – complementary information on SoC

Medicine	Price per package	Reference	Share of patients	Comment / Reference
Ramipril	31.00	Ramipril "Krka" 5 mg, 30 stk. (blister)	XXXX%	Based on share receiving ACEi or

		tabletter, Varenummer 091071		ARB in VALIANT OLP (XXXX%), in model assuming XX% of each
Losartan	17.40	Losartan "Stada" 100 mg, 100 stk. (blister) filmovertrukne tabl, Varenummer 599798	XXXX%	
Mycophenolate mofetil	537.00	Mycophenolatmofetil "Accord", 250 mg, 300 tablets, Varenummer 432712	XXXX%	VALIANT OLP
Tacrolimus	2 894.25	Adport, 5 mg, 50 tablets, Varenummer 439393	XXXX%	
Mycophenolic acid	1 685.03	Myfortic, 360 mg, 120 tablets, Varenummer 015755	XXX%	
Azathioprine	54.55	Azatioprin "Viatris", 50 mg, 100 tablets, Varenummer 410643	XXX%	
Prednisolone	218.72	Dermipred, 20 mg, 100 tablets, Varenummer 512138	XXXX%	
Dapagliflozin	1051.00	Forxiga, 10 mg, 90 tablets, Varenummer 111041	XXXX%	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; OLP, open-label period

References: (Lægemiddelstyrelsen 2026a, Sobi 2025c)

11.1.2 Drug Costs for Subsequent Treatment

Not applicable.

11.2 Hospital Costs

11.2.1 Administration

Patients on pegcetacoplan are expected to have a first administration at a hospital clinic and receive training in self-administration. Patients self-administer subsequent doses at home. Hence, this is included as a one-off cost. The cost employed for the nephrologist visit is presented in Table 55. A one-off pump cost for pegcetacoplan in-home infusion was also included to a cost of XXXX DKK.

Table 55. Assumptions regarding administration costs

Route of administration	Diagnosis and procedure codes*	DRG group	Unit cost, DKK
Subcutaneous	DN189 (Kronisk nyreinsufficiens UNS)	11MA98	1 588.00 DKK

11.2.2 Disease Management

11.2.2.1 CKD and uPCR Health States

Resource use for disease management based on CKD stage was sourced from a Danish clinical expert. The estimates were collected for each CKD stage for patients with a uPCR-level of 1-3 g/g. The frequencies and durations, as well as DRG groups, unit costs and diagnosis codes are presented in Table 56.

Table 56. Assumptions regarding disease management costs

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 1)	XXXXXXXXXXX	XXXXXX**	DN181	11MA98	1 588.00 DKK
Hospitalisation in nephrology department (uPCR 1.0 – 3.0 | CKD 1)	X	X	DN181	11MA02	42 772.00 DKK
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 2)	XXXXXXXXX	XXXXXX**	DN182	11MA98	1 588.00 DKK
Hospitalisation in nephrology department (uPCR 1.0 – 3.0 | CKD 2)	X	X	DN182	11MA02	42 772.00 DKK
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 3)	XXXXXXXXXX	XXXXXX**	DN183	11MA98	1 588.00 DKK
Hospitalisation in nephrology department	XXXXXXXXXX	XXXXXX	DN183	11MA02	42 772.00 DKK

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
(uPCR 1.0 – 3.0 | CKD 3)					
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 4)	XXXXXXXXXXX	XXXXXX**	DN184	11MA98	1 588.00 DKK
Hospitalisation in nephrology department (uPCR 1.0 – 3.0 | CKD 4)	XXXXXXXXXXX	XXXXXX	DN184	11MA02	42 772.00 DKK
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 5)	XXXXXXXXXX	XXXXXX**	DN185	11MA98	1 588.00 DKK
Hospitalisation in nephrology department (uPCR 1.0 – 3.0 | CKD 5)	XXXXXXXXXX	XXXXXX	DN185	11MA02	42 772.00 DKK

*Include other patient information if relevant to the selection of DRG group; A = action diagnosis; P = procedure

** Assumption; not relevant for unit cost

Abbreviations: CKD, chronic kidney disease; DKK, Danish krona; N/A, not applicable; uPCR, urine protein creatine ratio.

The relations in healthcare resource use between patients within the same CKD stage but with different uPCR levels have been estimated in a study in the UK setting (NICE 2024)(Table 57). In addition, the relations were validated with a Danish clinical expert.

The resource use in Table 56 are combined with the relations presented in Table 57 to estimate the disease management costs based on CKD stage and uPCR-level.

Table 57. Disease management costs – resource use depending on uPCR level

uPCR (g/g)	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5
uPCR <1	1/7 * uPCR 1-3	1/7 * uPCR 1-3	1/7 * uPCR 1-3	1/7 * uPCR 1-3	Same as uPCR 1-3
uPCR >3	3.7 * uPCR 1-3	3.7 * uPCR 1-3	3.7 * uPCR 1-3	1.6 * uPCR 1-3	Same as uPCR 1-3

Note: For patients in stable disease, the same resource use as for patients with uPCR <1 is assumed

Reference: Calculated based on NICE (2024) and validated by Danish clinical expert (Sobi 2026). Calculations presented in Appendix L

11.2.2.2 Dialysis Health State

Dialysis procedural costs are derived using DRG and are presented in Table 58. 68.30% of patients on dialysis receive haemodialysis and 31.7% receive peritoneal dialysis (Davies 2024). In addition to the dialysis procedures, nephrologist visits and hospitalisations are included. The frequencies are based on Eriksson et al. (2016) and the costs are based on DRG 2026 (Sundhed.dk 2025). The weighted cost per cycle (3 months) is XXXXXX DKK. The weighted cost per year amounts to XXXXXXX DKK.

Table 58. Disease management costs used in the model – dialysis health state

Activity	Frequency	Unit cost [DKK]	DRG code; procedure code	Reference
Peritoneal dialysis procedure	XXXXXXXXXXXXXXX	6 154.00	11PR07; BJFD27	DRG 2026; Sundhed.dk (2025)
Nephrologist visit - peritoneal dialysis	XXXXXXXXXXXXXXXXX	1 588.00	11MA98	DRG 2026; Sundhed.dk (2025) Eriksson et al. (2016)
Hospitalisation - peritoneal dialysis	XXXXXXXXXXXXXXXX	42 772.00	11MA02	DRG 2026; Sundhed.dk (2025) Eriksson et al. (2016)
Haemodialysis procedure	XXXXXXXXXXXXXXXX	3 574.00	11PR08, BJFD20	DRG 2026; Sundhed.dk (2023)
Nephrologist visit - haemodialysis	XXXXXXXXXXXXXXXX	1 588.00	11MA98	DRG 2026; Sundhed.dk (2025) Eriksson et al. (2016)
Hospitalisation - haemodialysis	XXXXXXXXXXXXXXXX	42 772.00	11MA02	DRG 2026; Sundhed.dk (2025) Eriksson et al. (2016)

Abbreviations: DKK, Danish krona

11.2.2.3 Transplant Health State

The resource use in the transplant health state (including post-transplant costs) includes the transplant procedure, as well as nephrologist visits and transplant maintenance treatment. The transplant maintenance treatment consists of immunosuppressants for which the doses are increased in association with a transplant compared to normal SoC (Sobi 2026). The cost of the transplant procedure was sourced using DRG, while the additional resource use was based on Nordic clinical expert input (Sobi 2026), and costed as presented in Table 59. The total cost equals 421 149 DKK.

Table 59. Disease management costs used in the model – transplant health state

Activity	Frequency	Unit cost [DKK]	DRG code; diagnosis code; procedure code	Reference
Transplant procedure	XXXXXXXXXXX	392 264.00	11MP01; DN185; KKAS10	DRG 2026
Nephrologist visit	XXXXXXXXX	1588.00	11MA98; DN181	Konsultation (DMC 2024)
Mycophenolate mofetil	XXXXXXXXXXXXX	537.00	N/A	Mycophenolatmofetil "Accord", 250 mg, 300 tablets, Varenummer 432712 (Lægemiddelstyrelsen 2026d)
Tacrolimus	XXXXXXXXXX	2894.25	N/A	Adport, 5 mg, 50 tablets, Varenummer 439393 (Lægemiddelstyrelsen 2026b)

Abbreviations: DKK, Danish krona; N/A, not applicable

11.2.3 Treatment Monitoring

Treatment monitoring is covered during the disease management visits (section 11.2.2.1).

Table 60. Assumptions regarding costs for treatment monitoring

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost

*Include other patient information if relevant to the selection of DRG group; A = action diagnosis; P = procedure.

11.2.4 Management of adverse events

Data from VALIANT's randomised control period highlights that only XXX TEAEs in each trial arm were considered serious (Appendix E) and therefore would have led to additional healthcare-related costs borne by the healthcare provider. Of these XX serious TEAEs, no single adverse event occurred in ≥5% of the trial population. Moreover, there were no differences in AEs between arms. In light of this, the model does not include any AE-related costs. Hence, Table 61 is not applicable.

Table 61. Assumptions regarding costs for management of adverse events

Adverse event	Proportion		Diagnosis codes*	DRG group	Unit cost
	[Intervention]	[comparator]			

*Include relevant procedure codes and other patient information if relevant for the selection of DRG group; A = action diagnosis; B = secondary diagnosis.

11.2.5 Other Hospital Costs

The model includes costs for cardiovascular events to capture the resource use associated with the increased risk for patients with CKD (Section 8.1). The one-off event costs were sourced using DRG 2026 (Sundhedsdatastyrelsen 2026) and are presented in Table 62.

Table 62. Cost associated with management of cardiovascular events

	DRG code; diagnosis code; procedure code	Unit cost/DRG tariff
Myocardial infarction	05MP32; DI219; KFNG05A	126 388.00
Acute Stroke	01MP12; DI639, BOHA1	38 246.00
Post-stroke	01PR02; BAXY1; N/A	6 635.00
Heart failure	05MA04; DI509; ZZ318	43 078.00

Reference: (Sundhedsdatastyrelsen 2026)

11.3 Patient Costs

The cost associated with patient time is included in the analysis and is valued at 200 DKK/hour, in line with the Danish Medicines Council's guidelines. In addition, the cost of transportation is included using a cost of 150 DKK/visit. The assumptions made regarding patient time are presented in Table 63. No patient time is included for hospitalisations,

transplantations or dialysis, due to the severity of the disease in those situations, in line with DMC guidelines.

Table 63. Assumptions regarding patient time

Activity	Frequency of activity	Time spent on activity	Transport time	Note
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 1)	XXXXXXXXXX	1 hour	90 minutes	
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 2)	XXXXXXXXX	1 hour	90 minutes	
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 3)	XXXXXXXXXX	1 hour	90 minutes	
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 4)	XXXXXXXXXX	1 hour	90 minutes	
Nephrologist visit (uPCR 1.0 – 3.0 | CKD 5)	XXXXXXXXX	1 hour	90 minutes	
Peritoneal dialysis	XXXXXXXXXXX	-	90 minutes	
Haemodialysis	XXXXXXXXXXXX	-	90 minutes	
Transplant procedure	XXXXXX	-	90 minutes	
Nephrologist visit (post transplant)	XXXXXXXX	-	90 minutes	

11.4 Other Costs

The cost savings for the healthcare system due to the reduced demand for kidney transplants for patients on pegcetacoplan are included in the model (section 9.5.1).

12. Results

The base case results are presented in Table 64. Despite pegcetacoplan treatment being associated with greater drug acquisition costs, it on average leads to cost savings of XXXXXXXX DKK compared to SoC only. This, due to the difference in disease management costs, as well as the cost savings to the healthcare system resulting from fewer patients on pegcetacoplan needing kidney transplants (XXX in the pegcetacoplan arm vs XXX in the SoC only arm) and hence enabling other patients to be transplanted instead of remaining on dialysis. The value of saved kidneys is also reflected in the number of QALYs. This, in addition to pegcetacoplan treatment being associated with additional life

years ([redacted]) and a greater share of time in less progressed health states, lead to pegcetacoplan treatment being associated with [redacted] additional QALYs compared to treatment with SoC only. Pegcetacoplan treatment is hence associated with [redacted].

Table 64. Results, discounted estimates, half-cycle corrected (where relevant), and adjusted for background mortality

	Pegcetacoplan	SoC only	Difference
Drug costs	[redacted]	[redacted]	[redacted]
Drug costs for subsequent treatment	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]
Treatment monitoring	[redacted]	[redacted]	[redacted]
Management of adverse events	[redacted]	[redacted]	[redacted]
Patient time	[redacted]	[redacted]	[redacted]
Cardiovascular and renal event costs	[redacted]	[redacted]	[redacted]
Cost value of saved kidneys	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
Number of kidney transplants (undiscounted)	[redacted]	[redacted]	[redacted]
QALYs in CKD1	[redacted]	[redacted]	[redacted]
QALYs in CKD2	[redacted]	[redacted]	[redacted]
QALYs in CKD3	[redacted]	[redacted]	[redacted]
QALYs in CKD4	[redacted]	[redacted]	[redacted]
QALYs in CKD5	[redacted]	[redacted]	[redacted]

	Pegcetacoplan	SoC only	Difference
QALYs in transplant	XXX	XXX	XXX
QALYs in haemodialysis	XXX	XXX	XXX
QALYs in peritoneal dialysis	XXX	XXX	XXX
QALY value of saved kidneys	XXX	XXX	XXX
Total QALYs	XXXX	XXXX	XXX
Incremental costs per life year gained	XXXXXXXX		
Incremental costs per QALY gained (ICER)	XXXXXXXX		

Table 65 is not applicable.

Table 65. Results per drug in combination treatments

	Drug costs

12.1 Sensitivity Analyses

12.1.1 Deterministic Sensitivity Analyses

The deterministic sensitivity analyses lead to XXXXXXXX results in XXX analyses. Hence, Table 66 is not populated.

Table 66. Results of deterministic sensitivity analyses

Deterministic sensitivity analysis	Incremental costs	Incremental QALYs	ICER

12.1.2 Probabilistic Sensitivity Analyses (PSA)

A scatterplot displaying the probabilistic sensitivity analyses is presented in Figure 10. As can be seen, all of the simulations are in the XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.

Figure 10. Scatterplot of probabilistic sensitivity analyses

Abbreviations: QALY: quality-adjusted life year; WTP: willingness to pay

In Figure 11, the associated cost-effectiveness acceptability curve is displayed.

Figure 11. Cost-effectiveness acceptability curve of probabilistic sensitivity analyses

Abbreviations: CE: cost-effective; DKK: Danish crown

In Figure 12, a convergence plot is presented.

Figure 12. Convergence plot of probabilistic sensitivity analyses

Abbreviations: Incremental cost-effectiveness ratio

13. Budget Impact Analysis

The budget impact of introducing pegcetacoplan was calculated based on the expected number of patients and patient uptake provided in Section 3.1.2. In the scenario without recommendation of pegcetacoplan, all XX patients are assumed to receive SoC only throughout the 5 years. In the scenario with recommendation, pegcetacoplan are assumed to gradually increase in uptake and reach 100% in year 5. The results of the budget impact analysis are presented in Table 67.

Table 67. Budget impact (undiscounted estimates), million DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Regional costs of recommendation					
Drug costs	XX	XX	XX	XX	XX
Other regional hospital costs	X	X	X	X	X
Total by recommendation	XX	XX	XX	X	X
Regional costs of non-recommendation					
Drug costs	X	X	X	X	X
Other regional hospital costs	X	X	X	X	X
Total for non-recommendation	X	X	X	X	X
Total budget impact	XX	XX	X	X	X

14. List of Experts

Name	Job function	Workplace
Prof. Stefan Jacobson	Professor	Division of Nephrology, Danderyd University Hospital, Stockholm Department of Clinical Sciences, Karolinska Institute, Stockholm
Assoc. Prof. Per Ramløv Ivarsen	Associate professor	Department of Medicine and Nephrology, Aarhus University Hospital, Aarhus
Jon Waarst Gregersen	Physician, Clinical Associate Professor	Department of Nephrology, Centre for SLE and Vasculitis Aalborg University Hospital, Aalborg

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Appendix A. Study Characteristics

Table 68. Main characteristics of included studies

Study name: VALIANT	**NCT number: NCT05067127**
Purpose	To assess the efficacy and safety of twice-weekly subcutaneous (SC) doses of pegcetacoplan compared to placebo in patients with C3 glomerulopathy (C3G) or immune-complex membranoproliferative glomerulonephritis (IC-MPGN) on the basis of a reduction in proteinuria.
Publications – title, author, journal, year	Fakhouri F, Bomback AS, Ariceta G, Delmas Y, Dixon BP, Gale DP, Greenbaum LA, Han SH, Isbel N, Le Quintrec M, Licht C, Mastrangelo A, Mizuno M, Neves de Holanda MI, Pickering MC, Remuzzi G, Van De Kar N, Vivarelli M, Walker PD, Wallace D, Zecher D, Francois C, Deschatelets P, Li L, Wang Z, Abad-Franch L, Kinnman N, López-Lázaro L, Szamosi J, Nester CM; VALIANT Trial Investigators Group. Trial of Pegcetacoplan in C3 Glomerulopathy and Immune-Complex MPGN. N Engl J Med. 2025 Dec 4;393(22):2210-2220. doi: 10.1056/NEJMoa2501510.
Study type and design	Phase 3 randomised, placebo-controlled, double-blinded, multicenter clinical study. Participants who met all of the inclusion criteria were randomly assigned in a 1:1 ratio to either the pegcetacoplan treatment arm or the placebo treatment arm. To achieve balance between the arms, two stratification factors were applied to the randomisation.
Number of trial participants (N)	124
Primary inclusion criteria	• Confirmatory diagnosis based on renal biopsy • uPCR ≥1.0 g/g; eGFR ≥30 mL/min/1.73 m^2 • Stable treatment (e.g., angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARBs], oral corticosteroids) for at least 12-weeks Active disease (2+ C3c staining in baseline biopsy or plasma / serum biomarkers indicative of complement dysregulation)
Primary exclusion criteria	• C3G and IC-MPGN secondary to another condition • Severe infection, malignancy, or prior diagnosis of HIV, HBV or HCV Absolute neutrophil count <1000 cells/mm^3
Intervention	Subcutaneous infusion of 20 mL (1080 mg) pegcetacoplan, twice weekly (for adults or adolescents >50 kg), and the three other weight-based doses either of 10 mL (540 mg), 12 mL (648 mg), or 15 mL (810 mg) N=63

Study name: VALIANT	NCT number: NCT05067127
Comparator(s)	Subcutaneous infusion of either 10 mL, 12 mL, 15 mL, or 20 mL, placebo (a sterile solution of 10 mM acetate buffer, pH 5.0, containing 4.1% sorbitol) twice weekly N=61
Follow-up time	After the 52 weeks treatment period, patients who did not enrol into a long-term extension study entered an 8-week follow-up period.
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary efficacy endpoint was the log-transformed ratio of uPCR at Week 26 compared to baseline. Further secondary endpoints included in this application are listed below: • The proportion of participants who met the criteria for achieving a composite renal endpoint (a stable or improved eGFR compared to the baseline visit (≤15% reduction in eGFR), and a ≥50% reduction in uPCR compared to the baseline visit.) • The proportion of participants with a reduction of at least 50% from baseline in uPCR • For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index score • The proportion of participants with evaluable renal biopsies which showed a decrease in C3c staining on renal biopsy from baseline • Change from baseline in eGFR • The change from baseline in EQ-5D-5L score **Other endpoints:** • The proportion of participants achieving proteinuria <1 g/day • For participants with serum albumin levels below the lower limit of normal at baseline, the proportion of participants with normalisation of serum albumin levels • For participants with serum C3 levels below the LLN at baseline, the proportion of participants with serum C3 levels above the LLN • The change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score • The change from baseline in Kidney Disease Quality of Life score • The change from baseline in WPAI score All endpoints above were also evaluated at Week 52 as exploratory endpoints.

Study name: VALIANT	NCT number: NCT05067127
	Safety Endpoints: • Incidence and severity of treatment-emergent adverse events (TEAEs) • Change from baseline in vital signs measurements, clinical laboratory tests, and electrocardiogram results • Number and incidence of rejection episodes (post-transplant participants only) • Number and incidence of graft loss (post-transplant participants only) • Incidence of death, stratified by transplant history
Analysis method	Longitudinal assessments for changes from baseline in continuous outcomes were analysed using a MMRM. Binary outcomes were analysed using a logistic regression model. ANCOVA was used to analyse C3G histologic index activity score, FACIT-Fatigue Scale score, and KDQoL score with treatment as a fixed effect, adjusted for baseline score of the endpoint, disease type, and stratification factors. For slope analysis of continuous outcomes, a mixed-effects model using the baseline and all postbaseline assessments were used and included treatment group, disease type, baseline immunosuppressants use (to add this effect for primary endpoint analysis only), and stratification factors as fixed effects, time (study week, continuous assuming linearity), and the time-by-treatment interaction. A common unstructured covariance matrix was used.
Subgroup analyses	Subgroup analyses were pre-specified and included 1) Age (adolescent [12-17 years] or adults), 2) disease type (C3G or IC-MPGN), 3) transplant status (no transplant or post-transplant recurrence), 4) Baseline FMU uPCR group (<3 g/g or ≥3 g/g), 5) baseline eGFR (<60 mL/min/1.73 m^2 or ≥60 mL/min/1.73 m^2), 5) immunosuppression status (yes or no). Analyses were performed as described in ''Method of analyses'', depending on the investigated endpoint.
Other relevant information	None.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; KDQoL, Kidney Disease Quality of Life; MMRM, mixed-effect model for repeated measures; SC, subcutaneous; TEAE, treatment-emergent adverse events; uPCR, urine protein creatinine ratio

Source: (clinicaltrials.gov 2025, Sobi 2024b, Sobi 2024c)

Appendix B. Results for Clinical effectiveness per Study

Table 69. Results per study

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
Change from baseline in log-transformed uPCR, LS mean (Week 26)	Pegcetacoplan	63	XXXX (XXXX, XXXX)	XXXX	XXXX, XXXX	XXXXX	XX	XX	XX	Changes from baseline were analysed using a MMRM. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% CIs.	(Sobi 2024a, Sobi 2024b)
	Placebo	61	XXXX (XXXX, XXXX)								
Change from baseline in log-transformed uPCR, LS	Pegcetacoplan	63	XXXX (XXXX, XXXX)	XXXX	XXXX, XXXX	XX	XX	XX	XX	Changes from baseline were analysed using a MMRM. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% CIs.	(Sobi 2025c, Sobi 2024b)
	Placebo	61	XXXX (XXXX, XXXX)								

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
mean (Week 52)											
Proportion of participants achieving	Pegcetacoplan	63	0.49 ([redacted], [redacted])	[redacted]	[redacted], [redacted]	[redacted]	[redacted]: [redacted]	[redacted], [redacted]	[redacted]	Binary outcomes were analysed using a logistic regression model. Statistical tests were	(Sobi 2024a, Sobi 2024b, Fakhouri et al. 2025b)

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
the composite renal endpoint (Week 26)	Placebo	61	0.034 ([redacted], [redacted])							performed at 2-sided 5% level of significance and CIs were two-sided 95% Cis.	

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
Proportion of participants achieving the composite renal endpoint, n (%) (Week 52)	Pegcetaclan	63	XX (XXX)	X (XXX)	XX	XX	XX	XX	XX	Binary outcomes were analysed using a logistic regression model. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% Cis.	(Sobi 2025c, Sobi 2024b)
	Placebo	61	XX (XXXX)								
Proportion of participants with a reduction of at least 50% from	Pegcetaclan	63	XXXX (XXXX, XXXX)	XXXX	XXXX, XXXX	XX	XX: XXXXX	XXXX, XXXXX	XXXXX	Binary outcomes were analysed using a logistic regression model. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% Cis.	(Sobi 2024a, Sobi 2024b, Fakhouri et al. 2025b)

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
baseline in uPCR (Week 26)	Placebo	61	XXXX (XXXX, XXXX)								
Proportion of participants with a reduction of at least 50% from baseline in uPCR, n (%) (Week 52)	Pegcetacoplan	63	XX (XXXX)	X (XXXX)	XX	XX	XX	XX	XX	Binary outcomes were analysed using a logistic regression model. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% Cis.	(Sobi 2025c, Sobi 2024b)
	Placebo	61	XX (XXXX)								
Change from baseline in	Pegcetacoplan	63	−1.497 (XXXX, XXXX)	XXXX	XXXX, XXXXX	XXXXX	XXX	XX	XX	Changes from baseline were analysed using a MMRM. Statistical tests were performed at 2-sided	(Sobi 2024a, Sobi 2024b, Fakhouri et al. 2025b)

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
eGFR, LS mean (Week 26)										5% level of significance and CIs were two-sided 95% CIs.	
	Placebo	61	−7.808 ([redacted], [redacted])								
Change from baseline in eGFR, LS mean (Week 52)	Pegcetacoplan	63	[redacted] ([redacted], [redacted])	[redacted]	[redacted], [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Changes from baseline were analysed using a MMRM. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% CIs.	(Sobi 2025c, Sobi 2024b)
	Placebo	61	[redacted] ([redacted], [redacted])								
Change from baseline in the activity score of	Pegcetacoplan	63	−3.482 ([redacted], [redacted])	[redacted]	[redacted], [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ANCOVA was used to analyse C3G histologic index activity score with treatment as a fixed effect, adjusted for baseline score	(Sobi 2024a, Sobi 2024b, Fakhouri et al. 2025b)

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
the C3G Histologic Index, LS mean (Week 26)										of the endpoint, disease type, and stratification factors. LS means were presented for each treatment group, along with the between treatment difference and 95% CI.	
	Placebo	61	−2.480 ([redacted], [redacted])								
Proportion of participants who showed decreases in C3c	Pegcetacoplan	63	[redacted] ([redacted], [redacted])	[redacted]	[redacted], [redacted]	[redacted]	[redacted]: [redacted]	[redacted], [redacted]	[redacted]	Binary outcomes were analysed using a logistic regression model. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% Cis.	(Sobi 2024a, Sobi 2024b)

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
staining from baseline (Week 26)	Placebo	61	XXXX (XXXX, XXXX)								
Proportion of participants achieving proteinuria <1 g/day (Week 26)	Pegcetacoplan	63	XXXX (XXXX, XXXX)	XXXX	XXXX, XXXX	XX	XX: XXXX	XXXX, XXXXX	XXXXX	Binary outcomes were analysed using a logistic regression model. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% Cis.	(Sobi 2024a, Sobi 2024b)
	Placebo	61	XXXX (XXXX, XXXX)								
Proportion of participants achieving normalisati	Pegcetacoplan	63	XXXX (XXXX, XXXX)	XXXX	XXXX, XXXX	XX	XX: XXXXX	XXXX, XXXXXX	XXXXX	Binary outcomes were analysed using a logistic regression model. Statistical tests were performed at 2-sided 5%	(Sobi 2024a, Sobi 2024b)

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
on of serum albumin levels (Week 26)										level of significance and CIs were two-sided 95% Cis.	
	Placebo	61	XXXX (XXXX, XXXX)								
Proportion of participants with baseline serum C3 levels below the LLN who achieve serum C3 levels above the LLN	Pegcetacoplan	63	XXXX (XXXX, XXXX)	XXXX	XXXX, XXXX	XX	XX: XXXXXX	XXXXX, XXXXXXX	XXXXX	Binary outcomes were analysed using a logistic regression model. Statistical tests were performed at 2-sided 5% level of significance and CIs were two-sided 95% Cis.	(Sobi 2024a, Sobi 2024b)
	Placebo	61	XXXX (XXXX, XXXX)								

Results of VALIANT (NCT05067127)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
(Week 26)											

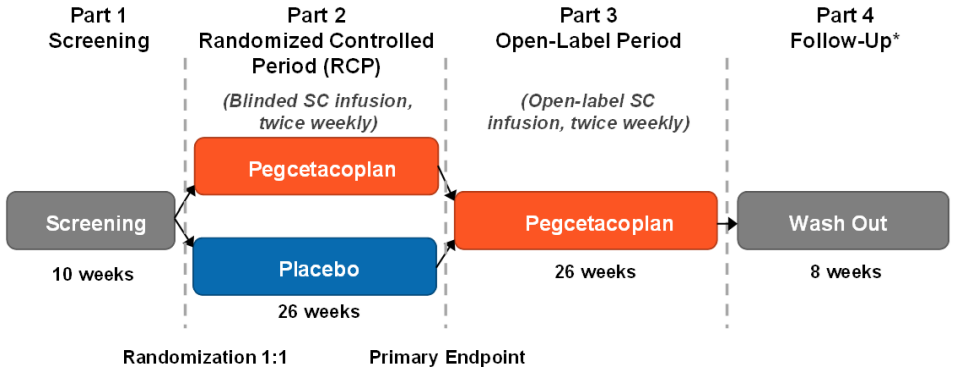
Abbreviations: C3G, C3 glomerulopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; LLN, lower limit of normal; MMRM, mixed-effect model for repeated measures; NR, not reported; OR, odds ratio; uPCR, urine protein creatine ratio

B.1 VALIANT (NCT05067127)

B.1.1 Study design

The VALIANT study was a phase 3, randomised, placebo-controlled, double-blinded, multicentre study and designed to assess the efficacy and safety of pegcetacoplan in patients with C3G or IC-MPGN. The influence of pegcetacoplan on quality of life was also assessed (Fakhouri et al. 2025b). The study design is depicted in Figure 13.

Figure 13. VALIANT study design



Abbreviations SC, subcutaneous; W, weeks

Source: (Sobi 2024a)

B.1.2 Patient Baseline Demographics and Disease Characteristics

Overall, VALIANT was generally representative of a real-world C3G or primary IC-MPGN population. Patient demographics and disease characteristics at baseline were generally similar and balanced between the treatment groups (Table 70 and Table 71). The overall mean (SD) age at screening was 26.0 (15.86) years, with a mean (SD) age of 28.2 (17.08) years and 23.6 (14.26) years in the pegcetacoplan group and placebo group, respectively. The age difference 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 (91 participants [73.4%]) and identified as Not Hispanic or Latino (88 participants [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 70) (Sobi 2024a).

Table 70. Baseline demographics (ITT Set)

	Statistics	Pegcetacoplan (n=63) n (%)	Placebo (n=61) n (%)	Overall (N=124) n (%)
Age at screening (years)	N	63	61	124

	Mean (SD)	28.2 (17.08)	23.6 (14.26)	26.0 (15.86)
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
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				
Male	n (%)	26 (41.3)	28 (45.9)	54 (43.5)
Female	n (%)	37 (58.7)	33 (54.1)	70 (56.5)
Race				
White	n (%)	45 (71.4)	46 (75.4)	91 (73.4)
Asian	n (%)	9 (14.3)	9 (14.8)	18 (14.5)
Black or African American	n (%)	1 (1.6)	0	1 (0.8)
American Indian or Alaskan Native	n (%)	1 (1.6)	0	1 (0.8)
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
Other	n (%)	7 (11.1)	6 (9.8)	13 (10.5)
Ethnicity				
Not Hispanic or Latino	n (%)	41 (65.1)	47 (77.0)	88 (71.0)
Hispanic	n (%)	15 (23.8)	10 (16.4)	25 (20.2)
Not reported[a]	n (%)	6 (9.5)	2 (3.3)	8 (6.5)
Unknown	n (%)	1 (1.6)	2 (3.3)	3 (2.4)

Body mass index (kg/m^2)	Mean (SD)	23.0 (5.2)	22.3 (4.6)	22.7 (4.9)

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

Source: (Sobi 2024a)

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 primary IC-MPGN underlying disease based on screening biopsy. Medical history characteristics were [redacted]. Indication per disease-specific medical history form was C3G for [redacted] participants ([redacted]%) in the pegcetacoplan group and [redacted] participants ([redacted]%) in the placebo group. For primary IC-MPGN, it was [redacted] participants ([redacted]%) in the pegcetacoplan group and [redacted] participants ([redacted]%) in the placebo group. Collection of medical history data showed that participants in the placebo group had [redacted] genetic risk factors for C3G/ primary IC-MPGN ([redacted]%) than participants in the pegcetacoplan group ([redacted]%). 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. Baseline proteinuria assessments (measured by 24-hour collection and triplicate FMU) were slightly higher in the pegcetacoplan group than in the placebo group. Mean (SD) baseline eGFR was slightly lower in the pegcetacoplan group (78.5 [34.12] mL/min/1.73 m^2) than the placebo group (87.3 [37.05] mL/min/1.73 m^2). Differences in baseline characteristics between treatment groups were not considered to be meaningful enough to have any impact on study outcomes (Table 71) (Sobi 2024a).

Table 71. Key baseline disease characteristics (ITT Set)

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

C3GN, n (%)	[redacted]	[redacted]	[redacted]
DDD, n (%)	[redacted]	[redacted]	[redacted]
Undetermined, n (%)	[redacted]	[redacted]	[redacted]
IC-MPGN, n (%)	[redacted]	[redacted]	[redacted]
Time since diagnosis (non-transplant) or most recent post-transplant recurrence (transplant) (year)			
All, median (range)	3.1 (0.3-18.4)	2.7 (0.0-18.6)	3.1 (0.0-18.6)
Adolescents, median (range)	3.8 (0.3-10.8)	2.7 (0.0-18.6)	3.4 (0.0-18.6)
Adult, median (range)	2.8 (0.4-18.4)	2.9 (0.3-13.8)	2.8 (0.3-18.4)
Prior kidney transplant, n (%)	5 (7.9)	4 (6.6)	9 (7.3)
Potential risk factors for C3G/IC-MPGN			
Genetic risk factors, n (%)	4 (6.3)	10 (16.4)	14 (11.3)
Autoantibodies, n (%)	12 (19.0)	9 (14.8)	21 (16.9)
Other, n (%)	8 (12.7)	8 (13.1)	16 (12.9)
Disease manifestations			
Oedema, n (%)	[redacted]	[redacted]	[redacted]
Fatigue, n (%)	[redacted]	[redacted]	[redacted]
Haematuria, n (%)	[redacted]	[redacted]	[redacted]
High blood pressure, n (%)	35 (55.6)	29 (47.5)	64 (51.6)
Hyperlipidaemia, n (%)	[redacted]	[redacted]	[redacted]
Nephrotic syndrome, n (%)	32 (50.8)	27 (44.3)	59 (47.6)
Proteinuria, n (%)	[redacted]	[redacted]	[redacted]
Reduced GFR, n (%)	[redacted]	[redacted]	[redacted]

Baseline 24h uPCR (mg/g), n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median	3151.00	2450.00	2861.00
Q1, Q3	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
Min, max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
Baseline triplicate FMU uPCR (mg/g), n	[redacted]	[redacted]	[redacted]
Mean (SD)	3123.78 (2408.324)	2540.75 (2014.620)	2836.97 (2233.627)
Median	2389.22	1815.56	2031.31
Q1, Q3	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
Min, max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
Baseline triplicate FMU uPCR by group (g/g)			
≥3 g/g, n (%)	24 (38.1)	16 (26.2)	40 (32.3)
1 to <3 g/g, n (%)	34 (54.0)	39 (63.9)	73 (58.9)
<1 g/g, n (%)	5 (7.9)	6 (9.8)	11 (8.9)
Baseline eGFR (mL/min/1.73 m^2), n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median	78.0	91.0	85.5
Q1, Q3	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
Min, max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
Baseline eGFR by group			
<60 mL/min/1.73 m^2, n (%)	21 (33.3)	20 (32.8)	41 (33.1)
≥60 mL/min/1.73 m^2, n (%)	42 (66.6)	41 (67.2)	83 (66.9)
Baseline serum creatinine (mg/dL), n	[redacted]	[redacted]	[redacted]

Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Baseline serum C3 (mg/dL), n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
C3c staining, OOM			
0, n (%)	0	0	0
1, n (%)	0	0	0
2, n (%)	12 (19.0)	10 (16.4)	22 (17.7)
3, n (%)	51 (81.0)	51 (83.6)	102 (82.3)
Baseline serum albumin (g/dL), n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]

Abbreviations: C3, complement 3; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; FMU, first-morning urine; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; ITT, intent-to-treat; OOM, orders of magnitude; SD, standard deviation; uPCR, urine protein creatinine ratio.

Source: (Sobi 2024a)

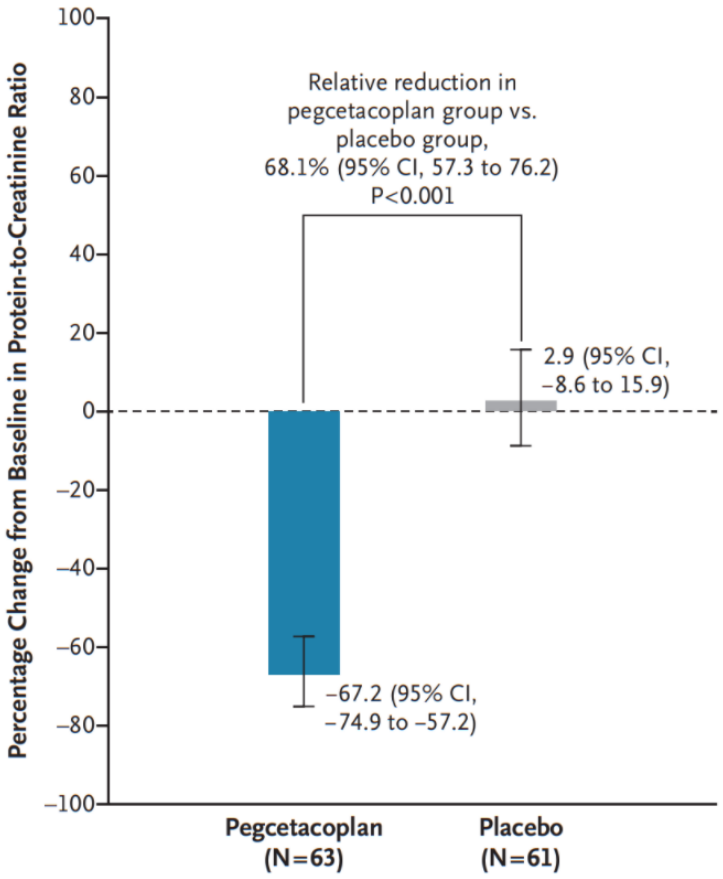
B.1.3 Primary Efficacy Outcome - Change from Baseline in Log-transformed uPCR

The primary efficacy endpoint in VALIANT was met, demonstrating the pegcetacoplan group had a statistically significant greater reduction from baseline in log-transformed FMU uPCR at Week 26 as compared to the placebo group (Table 72). The geometric mean (95% CI) of the ratio comparing FMU uPCR at Week 26 to baseline was [redacted],

[redacted]) for the pegcetacoplan group and [redacted] ([redacted], [redacted]) 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 −1.144 (95% CI −1.437, −0.851]; p<0.0001). This is equivalent to a relative reduction of 68.1% (95% CI 57.3, 76.2%) of pegcetacoplan compared to placebo (Figure 14) (Fakhouri et al. 2025b).

Proteinuria reduction with pegcetacoplan was observed as early as Week 4 (first sample collected after treatment initiation) and sustained through Week 26; proteinuria was largely unchanged with placebo (Sobi 2024a).

Figure 14. Change in uPCR at Week 26



Abbreviations: CI, confidence interval

Source: (Fakhouri et al. 2025b)

Table 72. Analysis of change from baseline in Log-transformed FMU uPCR with MMRM for RCP (ITT Set)

Week	Parameter	Pegcetacoplan (n=63)	Placebo (n=61)

Week 24-25-26[c]	[redacted][a]		
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
	[redacted]	[redacted]	
	[redacted][b]	[redacted]	[redacted]
	[redacted][b]	[redacted]	

[a] An MMRM model 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, is 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 is handled by hypothetical strategy, discontinuation of treatment is handled by treatment policy strategy.

[b] Geometric means and ratios are estimated by the exponentiated LS means and differences.

[c] The LS mean of Week 24-25-26 is estimated using a composite contrast of equal-weighted average over Week 24, 25, and 26.
Abbreviations: CFB, change from baseline; CI, confidence interval; FMU, first-morning urine; ITT, intent-to-treat; LS, least squares; MMRM, mixed models for repeated measures; RCP, randomised controlled period; SE, standard error; uPCR, urine protein creatinine ratio.

Source: (Sobi 2024a)

Analyses of the primary efficacy endpoint at Week 26 by subgroup were performed to evaluate the consistency of the primary analysis results across subgroups defined by demographic and baseline characteristics.

This supportive analysis showed that pegcetacoplan treatment resulted in significantly greater reductions in uPCR relative to placebo at Week 26 across all predefined subgroups examines. The results were consistent across all subgroups based on disease type (C3G vs primary IC-MPGN), age (adult vs adolescent), transplant history (non-transplant vs post-transplant recurrence), baseline immunosuppressant use, baseline uPCR, baseline eGFR, and baseline serum C3. These results further support the robustness of the results from the primary endpoint.

B.1.4 Key Secondary Outcome - Proportion of Participants Achieving the Composite Renal Endpoint

A participant met the requirements of the composite renal endpoint at Week 26 if they:

Had a stable or improved eGFR at Week 26 compared to baseline (≤15% reduction in eGFR), and

Had a ≥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 (49.21% in the pegcetacoplan group vs 3.28% in the placebo group) (Table 73) (Sobi 2024a, Fakhouri et al. 2025b). There was a 27-fold increase (OR: 27.479; 95% CI: 6.097-123.846; *P* <.0001) in the odds of participants meeting this composite endpoint at Week 26 with pegcetacoplan treatment vs placebo (Sobi 2024a).

Table 73. 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)
Participants who achieved the composite renal endpoint, n (%)	31 (49.21)	2 (3.28)
Participants with stable or improved eGFR compared to baseline (≤15% reduction in eGFR), n (%)	[redacted]	[redacted]
Participants with ≥50% reduction in uPCR compared to baseline, n (%)	38 (60.32)	3 (4.92)
Estimates/comparisons at Week 26		
Proportion (SE)	[redacted]	[redacted]
95% CI of proportion	[redacted]	[redacted]
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	[redacted]	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	[redacted]	
p-value (pegcetacoplan vs placebo)	<0.0001	

Abbreviations: C3G, complement 3 glomerulopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least squares; SE, standard error; uPCR, urine protein creatinine ratio.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

Subgroup analyses were performed to evaluate the consistency of the treatment effect of pegcetacoplan on the composite renal endpoint (defined as a key secondary endpoint) by subgroups of disease type (C3G and IC-MPGN), age (adolescents and adults), and transplant history (post-transplant and non-transplant). The comparative analysis of the composite renal endpoint at Week 26 within each subgroup showed overall consistent values with the overall ITT set, supporting that the treatment effect of pegcetacoplan was consistent across subgroups (Sobi 2024a).

B.1.5 Key Secondary Outcome - 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 (60.32% of participants in pegcetacoplan compared to 4.92% of participants in placebo) (Fakhouri et al. 2025b, Sobi 2024a). There was a 31-fold increase (OR 30.901; 95% CI 8.393, 113.772; p<0.0001) in the odds of participants achieving a 50% reduction in uPCR at Week 26 with pegcetacoplan treatment vs placebo (Table 74) (Sobi 2024a).

Table 74. Analysis of proportion of participants who achieved a reduction of ≥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 ≥50% reduction in uPCR compared to baseline (n [%])	38 (60.32)	3 (4.92)
Estimates/comparisons at Week 26		
Proportion (SE)	[redacted]	[redacted]
95% CI of proportion	[redacted]	[redacted]
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	[redacted]	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	[redacted]	
p-value (pegcetacoplan vs placebo)	<0.0001	

Abbreviations: CI, confidence interval; FMU, first-morning urine; ITT, intent-to-treat; SE, standard error; uPCR, urine protein creatinine ratio.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

Subgroup analyses were performed to evaluate the consistency of the treatment effect of pegcetacoplan on the secondary endpoint of a reduction of at least 50% from baseline uPCR for key subgroups of disease type (C3G and IC-MPGN), age (adolescents and adults), and transplant history (post-transplant and non-transplant). Pegcetacoplan treatment was shown to result in a higher proportion of participants achieving a reduction of at least 50% in FMU uPCR at Week 26 than placebo regardless of disease type, age, and transplant history, supporting that the treatment effect of pegcetacoplan was consistent (Sobi 2024a).

B.1.6 Key Secondary Outcome - Change from Baseline in the Activity Score of the C3G Histologic Index

Renal biopsy was required for enrolment (baseline) and at Week 26 for adults but was not mandatory for adolescents. 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 (LS mean [95% CI] of change from baseline in the pegcetacoplan group was −3.482 [−4.721, −2.244] compared to −2.480 [−3.775, −1.186] in the placebo group; adjusted mean difference [95% CI] −1.002 [−2.803, 0.798], p=0.2753) (Table 75) (Sobi 2024a, Fakhouri et al. 2025b).

Table 75. Analysis of change from baseline to Week 26 in C3G Histologic Index Activity 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)	−3.482 (XXXXX)	−2.480 (XXXXX)
95% CI of LS mean	(−4.721, −2.244)	(−3.775, −1.186)
Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	−1.002 (−2.803, 0.798)	
Percentage Difference (pegcetacoplan vs placebo)	XXXXX	
p-value (pegcetacoplan vs placebo)	0.2753	

Abbreviations: ANCOVA, analysis of covariance; C3G, complement 3 glomerulopathy; CI, confidence interval; ITT, intent-to-treat; LS, least squares; SE, standard error.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

B.1.7 Key Secondary Outcome - Proportion of Participants who Showed Decreases in C3c Staining from Baseline

As described in Section B.1.6, renal biopsy was required for enrolment (baseline) and at Week 26 for adults.

A substantially larger proportion of participants had a reduction in C3c staining on kidney biopsy (defined as decrease of at least two orders of magnitude of intensity of immunofluorescence from baseline) at Week 26 with pegcetacoplan treatment (74.29%) compared to placebo treatment (11.76%) (Table 76) (Fakhouri et al. 2025b, Sobi 2024a). There was a 27-fold increase in the odds of patients meeting C3c reduction of at least two orders of magnitude of intensity at Week 26 vs placebo (XXXXXXXX; XXXXXXXXXXX, XXXXXX; XXXXXXXXXXXXX). Furthermore, 71.4% participants achieved C3c staining of zero in pegcetacoplan group vs only 8.8% in placebo group at Week 26. These findings demonstrate the disease-modifying effect of pegcetacoplan in preventing further deposition of C3 breakdown products in the glomeruli, thus preventing disease progression and affording the kidney the opportunity to clear existing deposits. Subgroup analyses were performed for this key secondary endpoint to evaluate the consistency of the results across the specified subgroups. Pegcetacoplan treatment was

shown to result in a consistently [redacted] proportion of participants achieving a C3c reduction of at least two orders of magnitude of intensity at Week 26 across subgroups examined (Sobi 2024a).

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 76. 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 (74.29)	4 (11.76)
Estimates/comparisons at Week 26		
Proportion (SE)	[redacted]	[redacted]
95% CI of proportion	[redacted]	[redacted]
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	[redacted]	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	[redacted]	
p-value (pegcetacoplan vs placebo)	[redacted]	

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LS, least squares; SE, standard error.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

B.1.8 Key Secondary Outcome – Change from Baseline in eGFR

The change in eGFR from baseline to the end of the 26-week RCP was substantially less in the pegcetacoplan group (reduction of 1.5 mL/min/1.73 m^2) than in the placebo group (reduction of 7.8 mL/min/1.73 m^2) demonstrating that eGFR stabilised with pegcetacoplan treatment (Table 77). At Week 26, the LS mean change (95% CI) in eGFR from baseline was −1.497 (−5.892, 2.899) mL/min/1.73 m^2 in the pegcetacoplan group compared to −7.808 (−11.570, −4.047) mL/min/1.73 m^2 in the placebo group. The LS mean difference (95% CI) was 6.312 (0.501, 12.122) mL/min/1.73 m^2 with a nominal p=0.0333, which demonstrates stabilisation of eGFR with pegcetacoplan treatment compared to placebo (Sobi 2024a, Fakhouri et al. 2025b).

Table 77. Analysis of change from baseline in eGFR (mL/min/1.73 m^2) 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		
	LS mean (SE)	−1.497 ([redacted])	−7.808 ([redacted])
	95% CI of LS mean	(−5.892, 2.899)	(−11.570, −4.047)
	Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	6.312 (0.501, 12.122)	
	Percentage difference (pegcetacoplan vs placebo)	−80.8	
	p-value (pegcetacoplan vs placebo)	[redacted]	

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least squares; MMRM, mixed models for repeated measures; SE, standard error.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

Overall, the LS mean changes in eGFR over time demonstrated [redacted] eGFR decline with pegcetacoplan treatment compared to placebo and, therefore, overall [redacted] of kidney function with pegcetacoplan treatment (Figure 15). 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 (Sobi 2024a).

Figure 15. Change in eGFR over 26 Weeks of treatment from the MMRM in the RCP (ITT Set)

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 analyse 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.

Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least squares; MMRM, mixed models for repeated measures; RCP, randomised controlled period; SE, standard error.

Source: (Sobi 2024a)

Subgroup analyses were performed for change from baseline in eGFR to evaluate the consistency of the results across the specified subgroups. The treatment effect of pegcetacoplan was generally consistent across all subgroups examined with the exception of participants with normal C3 at baseline. This subgroup finding was likely by chance and related to the low numbers, given that this subgroup behaved consistently with regard to the primary endpoint and other key secondary endpoints (Sobi 2024a).

B.1.9 Additional Secondary Outcomes

The additional secondary efficacy endpoints at Week 26 were analysed in the ITT set and are summarised in Table 78. P-values are all nominal and not controlled for multiplicity testing.

Table 78. 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 (%)	[redacted]	[redacted]	[redacted][a]
Proportion of participants with baseline serum albumin levels <LLN who achieve normalisation of serum albumin levels, n (%)	[redacted]	[redacted]	[redacted][a]
Proportion of participants with baseline serum C3 levels <LLN who achieve serum C3 levels above LLN, n (%)	[redacted]	[redacted]	[redacted]
Change in FACIT-Fatigue Scale score from baseline, LS mean (95% CI)	[redacted]	[redacted]	[redacted][b]

Change in KDQoL score from baseline, LS mean (95% CI)	[redacted]	[redacted]	[redacted] [b] [redacted]

[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 nonresponder. Participants with missing outcome values other than intercurrent events were regarded as nonresponder.

[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.

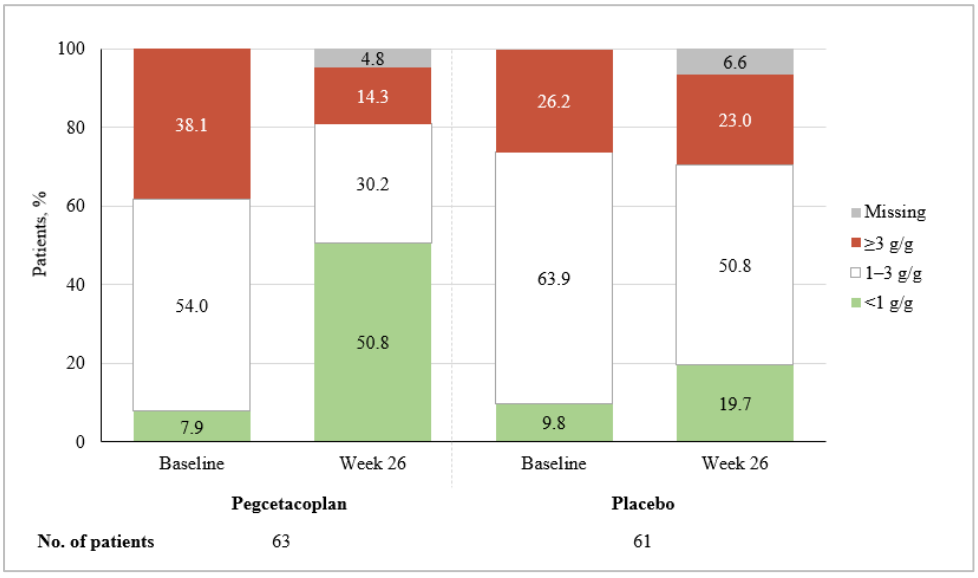
Abbreviations: C3, complement 3; CI, confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; ITT, intent-to-treat; KDQoL, Kidney Disease Quality of Life; LLN, lower limit of normal; LS, least squares.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

B.1.9.1 Proportion of Participants Achieving Proteinuria <1 g/day

Pegcetacoplan treatment resulted in significantly more participants achieving proteinuria <1 g/day at Week 26. The odds of participants meeting this endpoint were 5-fold greater with pegcetacoplan treatment than with placebo (OR 5.753; 95% CI 2.106, 15.716; p=0.0006). Proteinuria reduction with pegcetacoplan corresponded with a substantial increase in the proportion of patients with proteinuria <1 g/g after 26 weeks (7.9% at baseline vs 50.8% at Week 26) and a marked decrease in the proportion in the nephrotic range of ≥3 g/g (38.1% at baseline vs 14.3% at Week 26) (Fakhouri et al. 2025b).

Figure 16. Proteinuria shift from baseline to Week 26 in patients receiving pegcetacoplan or placebo



Source: adapted from (Fakhouri et al. 2025b)

In the original protocol for VALIANT, the endpoint for 24-hour urine collections was at Week 26 and Week 52. However, in VALIANT Protocol Amendment 1, the 26-Week endpoint was removed and 24-hour urine was obtained at screening visit 1 and Weeks 8, 24, 36, 48, and 60. Thus, the analysis of the proportion of participants achieving proteinuria <1 g/day was based on Week 24 data. Pegcetacoplan treatment resulted in more participants achieving proteinuria <1 g/day (measured by 24 hour urine) at Week 24 (Table 79). There was a 6-fold increase (OR pegcetacoplan vs placebo: 5.753 [95% CI: 2.106, 15.716]) in the odds of participants meeting this endpoint at Week 26 with pegcetacoplan treatment vs placebo (Sobi 2024a).

Table 79. Analysis of proportion of participants achieving proteinuria <1 g/day at Week 24 with logistic model by treatment group (ITT Set)

Parameter	Pecetacoplan (N=63)	Placebo (N=61)
Participants who achieved proteinuria <1 g/day, n (%)	23 (36.51)	7 (11.48)
Estimates/comparisons at Week 24		
Proportion (SE)	([redacted], [redacted])	([redacted], [redacted])
95% CI of proportion	[redacted]	[redacted]
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	[redacted] ([redacted])	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	5.753 (2.106-15.716)	
p-value (pegcetacoplan vs placebo)	[redacted]	

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 nonresponder. Participants with missing proteinuria values at Week 24 for reasons other than ICEs were regarded as nonresponder.

Abbreviations: ICE, intercurrent event; ITT, intent-to-treat.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

B.1.9.2 Proportion of Participants Achieving 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 [redacted] with pegcetacoplan treatment than with placebo ([redacted] [[redacted]%] vs [redacted] [[redacted]%]). The odds of meeting this endpoint were 88-fold [redacted] with pegcetacoplan treatment than with placebo (OR 88.341; 95% CI 8.863, 880.544; [redacted]) (Table 80) (Sobi 2024a, Fakhouri et al. 2025b).

Table 80. 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 (77.78)	1 (4.35)
Estimates/comparisons at Week 26		
Proportion (SE)	[redacted]	[redacted]
95% CI of proportion	[redacted]	[redacted]
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	[redacted]	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	88.341 (8.863, 880.544)	
p-value (pegcetacoplan vs placebo)	[redacted]	

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LLN, lower limit of normal; SE, standard error

Source: (Sobi 2024a, Fakhouri et al. 2025b)

B.1.9.3 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 [90.24%] in the pegcetacoplan group vs three participants [6.12%] in the placebo group) (Table 81) (Fakhouri et al. 2025b, Sobi 2024a).

Table 81. 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 (90.24)	3 (6.12)
Estimates/comparisons at Week 26		

Proportion (SE)	[redacted]	[redacted]
95% CI of proportion	[redacted]	[redacted]
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	[redacted]	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	>999.999 (12.175, >9999.999)	
p-value (pegcetacoplan vs placebo)	[redacted]	

Note: Notes: Baseline serum C3 value was calculated as the average of up to two 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 two 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 nonresponder. Participants with missing C3 levels at Week 26 for reasons other than ICEs were regarded as nonresponder.

Abbreviations: C3, complement 3; CI, confidence interval; ITT, intent-to-treat; LLN, lower limit of normal; SE, standard error.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

B.1.10 Outcome from the 52-Week Open-Label Period

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 (Figure 13, part 3). 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 follow-up period (Figure 13, part 4) unless they entered a long-term extension study (Study APL2-C3G-314).

Unless otherwise specified, all efficacy analyses were performed on the ITT set using data collected during the overall study period. All primary, key secondary, and additional secondary endpoints at Week 52 were evaluated as exploratory efficacy endpoints.

B.1.10.1 OLP - Disposition of Participants, Demographics and Baseline Characteristics

A total of [redacted] participants received ≥1 dose of study drug during the OLP: [redacted] participants continued pegcetacoplan from the RCP (i.e., pegcetacoplan-to-pegcetacoplan) and [redacted] participants changed to pegcetacoplan from placebo during the RCP (i.e., placebo-to-pegcetacoplan). During the OLP, the mean durations of treatment were similar between treatment groups: [redacted] days (range: [redacted] days) in the pegcetacoplan-to-pegcetacoplan group and [redacted] days (range: [redacted] days) in the placebo-to-pegcetacoplan groups. At a data cut-off of 12 February 2025, [redacted] participants remained on treatment at the cut-off date: n=[redacted] for pegcetacoplan-to-pegcetacoplan and n=[redacted] for placebo-to-

pegcetacoplan; [redacted] participants had discontinued study treatment during the OLP (n=[redacted] in both the pegcetacoplan-to-pegcetacoplan and placebo-to-pegcetacoplan groups) (Sobi 2025c).

For demographics and baseline characteristics, see Section B.1.

B.1.10.2 OLP - Change in Log-transformed uPCR at Week 52

The decrease in uPCR from baseline observed during the RCP was sustained through to Week 52 in the pegcetacoplan-to-pegcetacoplan group. The placebo-to-pegcetacoplan group experienced a rapid [redacted] in uPCR after beginning pegcetacoplan treatment (evident at Week 28, i.e., the first post-dose measurement after beginning pegcetacoplan treatment]) that continued and was [redacted] through to Week 52 (Table 82 and Figure 17). A 67.2% reduction in proteinuria between baseline and Week 52 was observed in the pegcetacoplan-to-pegcetacoplan group based on the geometric mean data ([redacted]; [redacted], [redacted]); this magnitude of change was similar to that observed in the pegcetacoplan group during the RCP. In the placebo-to-pegcetacoplan group, there was a 51.3% reduction in proteinuria from baseline to Week 52 based on the geometric mean ([redacted]; [redacted], [redacted]) (Sobi 2025c).

Table 82. Analysis of change from baseline in log-transformed FMU uPCR (mg/g) with MMRM for the overall study (ITT Set)

Estimated/comparisons[a]	Pegcetacoplan-to-pegcetacoplan (n=63)	Placebo-to-pegcetacoplan (n=61)
LS mean (SE)	[redacted]	[redacted]
95% CI of LS mean	[redacted]	[redacted]
Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	[redacted]	[redacted]
Geometric means (95% CI)[b]	[redacted]	[redacted]
Geometric means ratios (95% CI) (pegcetacoplan vs placebo)[b]	[redacted]	

[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 calculated as the average of the uPCR measurements from at least six of the 9 FMU samples collected between the start of screening and Day 1, inclusive.

Abbreviations: CI, confidence interval; FMU, first-morning spot urine; ITT, intent-to-treat; LS, least squares; MMRM, mixed-effects model for repeated measures; SE, standard error; uPCR, urine protein-to-creatinine ratio.

Source: (Sobi 2025c)

Figure 17. Geometric mean (95% CI) change from baseline in log-transformed FMU uPCR ratio (mg/g) by analysis visit and treatment group from MMRM for the overall study (ITT 52 Set)

Abbreviations: CI, confidence intervals; FMU, first-morning urine; MMRM, mixed-effect model for repeated measures; uPCR, urine protein-to-creatinine ratio.

Source: (Sobi 2025c)

B.1.10.3 OLP – Proportion of Participants who Achieved the Composite Renal Endpoint at Week 52

The proportion of participants in the pegcetacoplan-to-pegcetacoplan group who achieved the composite renal endpoint at Week 52 was XXX%. This compares with XXX% in the pegcetacoplan group during the RCP, indicating a sustained response during long-term pegcetacoplan treatment. In the placebo-to-pegcetacoplan group, XXX% of participants achieved the composite renal endpoint at Week 52 (Sobi 2025c). In contrast, only XXX% of placebo-treated participants achieved this endpoint during the RCP, demonstrating a clinically meaningful stabilisation of eGFR and reduction in proteinuria in response to starting treatment with pegcetacoplan in the OLP in this group (Sobi 2025c).

B.1.10.4 OLP - Proportion of Participants with ≥50% Reduction from Baseline in uPCR at Week 52

Compared with baseline, XX (XX%) participants in the pegcetacoplan-to-pegcetacoplan group and XX (XX%) participants in the placebo-to-pegcetacoplan group had a ≥50% reduction in uPCR at Week 52 (Sobi 2025c, Nester et al. 2025b). In contrast, only XX% of participants in the placebo group achieved a ≥50% reduction during the RCP, demonstrating a meaningful XXXXXXXXX in proteinuria in response to initiation of treatment with pegcetacoplan in the OLP (Sobi 2025c).

B.1.10.5 OLP - Change from Baseline in eGFR at Week 52

The change in eGFR from baseline to Week 52 was analysed for the overall ITT set and the OLP set using a MMRM.

In the ITT set, eGFR was stabilised through 52 weeks in the pegcetacoplan-to-pegcetacoplan group (Figure 18). After initially declining in the placebo-to-pegcetacoplan group, eGFR stabilised for the remainder of the treatment period after the initiation of pegcetacoplan. Slope analysis using piecewise linear mixed-effect model supported the main MMRM analysis. After 52 weeks, the LS mean reduction from baseline in eGFR was slightly greater in the placebo-to-pegcetacoplan group (Table 83). However, the magnitude of the difference was small and the confidence intervals for the treatment groups overlap, indicating that the between-group difference was not meaningful (Sobi 2025c).

In the OLP set, mean change (SD) from baseline at Week 52 was [redacted] ([redacted]) for the pegcetacoplan-to-pegcetacoplan group and [redacted] ([redacted]) for the placebo-to-pegcetacoplan group. The pegcetacoplan-to-pegcetacoplan group showed sustained stabilisation of eGFR, while the placebo-to-pegcetacoplan group showed eGFR stabilisation, different to the decline observed during the RCP (Sobi 2025c).

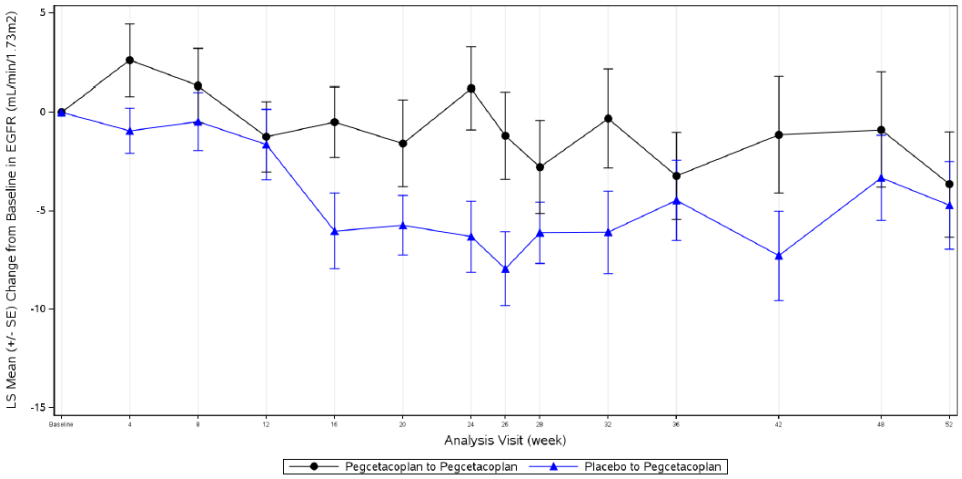
Table 83. Analysis of change from baseline in eGFR (mL/min/1.73 m²) with MMRM at Week 52 for the overall study (ITT Set)

Parameter	Pegcetacoplan-to-pegcetacoplan (n=63)	Placebo-to-pegcetacoplan (n=61)
LS mean (SE)	−3.651 ([redacted])	−4.720 ([redacted])
95% CI of LS mean	([redacted], [redacted])	([redacted], [redacted])
Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	[redacted] ([redacted], [redacted])	[redacted]
Percentage difference (pegcetacoplan vs placebo)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least squares; MMRM, mixed-effects model for repeated measures; SE, standard error.

Source: (Sobi 2025c)

Figure 18. LS mean (±SE) change from baseline in eGFR (mL/min/1.73 m^2) by analysis visit and treatment group from MMRM for overall study (ITT Set)



Note: Baseline eGFR value was calculated using the last non-missing assessment prior to first dose.
Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least squares; MMRM, mixed-effects model for repeated measures; SE, standard error.

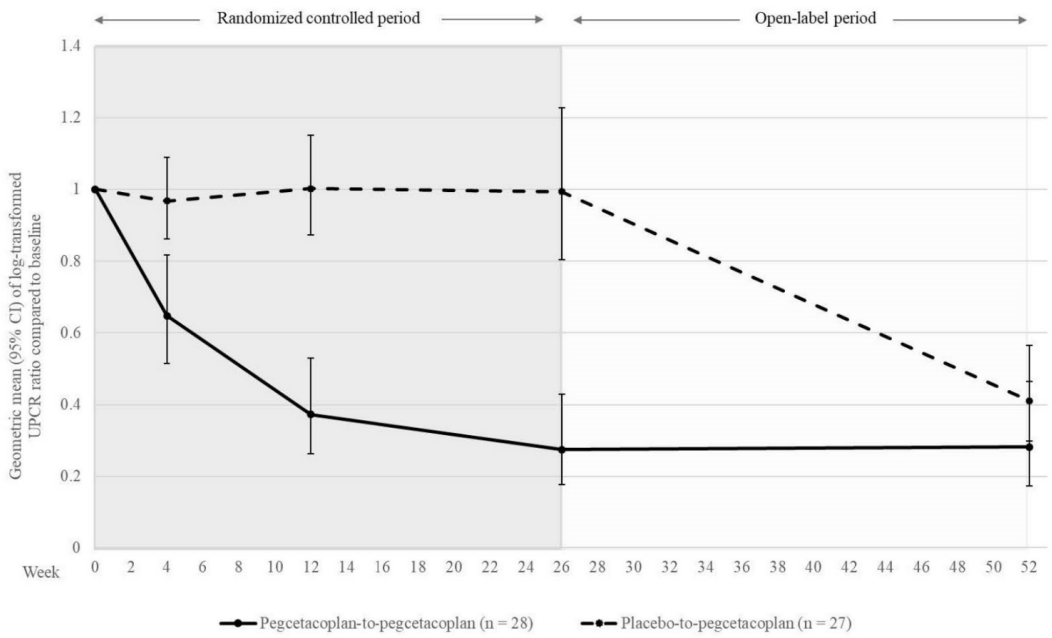
Source: (Bomback et al. 2024b)

B.1.10.6 Post hoc Analysis of Proteinuria Reduction and eGFR Stabilisation in Adolescents

A post hoc analysis investigated the reductions in proteinuria and stabilisation of eGFR in adolescents at Week 52 (Greenbaum et al. 2025). Most of the adolescent participants randomised to pegcetacoplan or placebo at the start of the RCP (28 and 27, respectively) entered the OLP (27 and 25, respectively). There was a sustained reduction in proteinuria in adolescents who received pegcetacoplan for 52 weeks: mean (95% CI) UPCR CFB was −73.6% (−83.1, −58.6) at Week 26 and −71.8% (−82.9, −53.6) at Week 52 (Figure 19). Adolescents who were randomised to placebo and received pegcetacoplan in the OLP had reductions in proteinuria that were consistent with the pegcetacoplan-to-pegcetacoplan group.

Adolescents also achieved stable eGFR during the 52-week treatment period. LS mean (SE) change in eGFR (mL/min/1.73^2) from baseline was 0.7 (3.6) at Week 26 and 3.2 (4.1) at Week 52. No new safety signals were observed. Overall, the data confirm that the efficacy of pegcetacoplan in adolescents is consistent with that observed in adults with C3G/IC-MPGN.

Figure 19. Change in proteinuria over time in adolescents



Abbreviations: CI, confidence interval; uPCR, urine protein creatine ratio.

Source: (Greenbaum et al. 2025)

Appendix C. Subsequent Treatment

Not applicable for this submission as no subsequent treatment exists after pegcetacoplan.

Appendix D. Comparative Analyses

Not applicable.

Table 84. Comparative analysis of studies comparing [intervention] with [comparator] for patients with [indication]

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P-value	Difference	CI	P-value		

Appendix E. Extrapolation of Patient Transitions

E.1 Parametric Extrapolation Models

Not applicable.

E.1.1 Extrapolation of [clinical endpoint 1]

E.1.1.1 Log-Cumulative Hazard Plots and Residual Plots

E.1.1.2 Internal validity

E.1.1.2.1 Assessment of Statistical and Visual Fit (AIC and BIC)

E.1.1.2.2 Assessment of Smoothed Hazard Functions

E.1.1.3 External Validity

E.1.1.4 Other Assumptions

E.1.2 Extrapolations of [clinical endpoint 2]

E.2 Transition Probabilities

E.2.1 Internal Validity

Not applicable.

E.2.2 External Validity

Not applicable.

E.2.3 Other Assumptions

To transform the estimates from the multinomial logistic regression model, presented in Table 30 into transition probabilities between uPCR health states, intermediary values were calculated as

[redacted]

Where a, b and c are binary values dependent on what should be included and HS 1 is uPCR<1 health state, HS 2 is uPCR 1.0-3.0 and HS 3 is uPCR >3.0. E.g. the intermediary value for HS 2 to HS 3 for pegcetacoplan would be calculated as:

[redacted]

If calculated for probabilities from HS 1, both a and b should be set to 0

Intermediary table for PEG:

Table 85. Intermediary table pegcetacoplan, uPCR transition probabilities

	From HS 1	From HS 2	From HS 3
To HS 2	[redacted]	[redacted]	[redacted]
To HS 3	[redacted]	[redacted]	[redacted]

Abbreviations: HS 1 = uPCR<1 health state, HS 2 = uPCR 1.0-3.0 health state, HS 3 = uPCR >3.0 health state

Intermediary table for SoC:

Table 86. Intermediary table SoC only, uPCR transition probabilities

	From HS 1	From HS 2	From HS 3
To HS 2	[redacted]	[redacted]	[redacted]
To HS 3	[redacted]	[redacted]	[redacted]

Abbreviations: HS 1 = uPCR<1 health state, HS 2 = uPCR 1.0-3.0 health state, HS 3 = uPCR >3.0 health state

To calculate final probabilities, the following equation is used:

[redacted]

Where i = 1,2,3 and j = 2,3. For example probability from HS 1 to HS 3 for pegcetacoplan is calculated as:

[redacted]

Movement to HS 1 is calculated as the complement of probabilities of moving to HS 2 and HS 3.

Appendix F. Serious Adverse Events

There was one death reported during the RCP (Fakhouri et al. 2025b). A 61-year-old White male participant 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 were

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

A summary of serious TEAEs by preferred term (PT) during the RCP (safety set) is presented in Table 87. In total, [redacted] participants had a serious TEAE during the RCP: [redacted] ([redacted]%) participants with [redacted] events in the pegcetacoplan group and [redacted] ([redacted]%) participants with [redacted] events in the placebo group.

The most common serious TEAE was acute kidney injury, which was reported by one participant in the pegcetacoplan group and two participants in the placebo group. No other specific serious TEAE (PT) was experienced by more than one participant.

[redacted] participant in the pegcetacoplan group had a serious TEAE (pyrexia) that was considered to be related to [redacted]. No other treatment-related serious TEAEs were reported (Sobi 2024a).

Table 87. Serious TEAEs by SOC and PT during the RCP (Safety Set)

SoC PT	Pegcetacoplan (N=63) n (%)	Placebo (N=61) n (%)
Any serious TEAEs	6 (9.5) [total events: 9]	6 (9.8) [total events: 10]
Infections and infestations	[redacted] ([redacted])	[redacted] ([redacted])
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	[redacted] ([redacted])	[redacted] ([redacted])
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	[redacted] ([redacted])	[redacted]
Pyrexia	1 (1.6)	0

Respiratory, thoracic and mediastinal disorders	X (XX)	X
Respiratory failure	1 (1.6)	0
Vascular disorders	X (XX)	X
Hypertension	1 (1.6)	0
Gastrointestinal disorders	X	X (XX)
Vomiting	0	1 (1.6)
Investigations	X	X (XX)
Blood creatinine increased	0	1 (1.6)
Pregnancy, puerperium and perinatal conditions	X	X (XX)
Abortion spontaneous	0	1 (1.6)
Pregnancy	0	1 (1.6)

Abbreviations: m, number of events; n, number of participants; PT, preferred term; RCP, randomised controlled period; SoC, system organ class; TEAE, treatment-emergent adverse event.

Source: (Sobi 2024a, Fakhouri et al. 2025b)

In total, 14 (11.7%) participants had an SAE during the overall study. The most common SAEs by SoC were infections and infestations (XX%), renal and urinary disorders (XX%), and injury, poisoning and procedural complications (XX%). By PT, the most common SAEs in the overall study were XXXXXXXXXXXXXXXXXX (XX%), XXXXXXXXXX (XX%), and XXXXXXX (XX%). No other specific SAE (by PT) was experienced by more than one participant during the overall study (Table 88).

There was one SAE of infection by encapsulated bacteria during the OLP (pneumonia due to *Streptococcus pneumoniae*); this event was assessed by the investigator as not related to pegcetacoplan. No infections caused by *Neisseria meningitidis* or *Haemophilus influenzae* type B were reported as SAEs.

Of the events listed below, the events of XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX (XXXXXXXXXXXX [XX%] in the placebo-to-pegcetacoplan group during the OLP), XXXXXXXXXXXXXXX (XXXXXXXXXXXX [XX%] in the pegcetacoplan-to-pegcetacoplan group during the OLP), and XXXXXXXXXXXXX (XXXXXXXXXXXX [XX%] in the pegcetacoplan-to-pegcetacoplan group during the OLP) XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. The XXX severe SAEs of herpes zoster meningoencephalitis was assessed as possibly related to XXXXXXXXXXXX by the investigator and not related to XXXXXXXXXXXX by the sponsor. An alternative explanation for the events of herpes zoster meningoencephalitis was mycophenolate mofetil immunosuppressive treatment. Lifelong immunosuppression to prevent organ rejection, leads to decreased cellular immunity and, in turn, an increased risk of

developing herpes zoster from reactivation of latent Varicella-Zoster virus. The events of renal impairment and renal failure were both assessed as not related to pegcetacoplan by the investigator (Table 88) (Sobi 2025c).

Table 88. SAEs by SOC and PT during the OLP and overall study (Safety Set)

Events by SOC and PT, n (%)	OLP			Overall (N=120)
	Pegcetacoplan-to-pegcetacoplan (n=61)	Placebo-to-pegcetacoplan (n=57)	Total (n=118)	
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster meningoencephalitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia pneumococcal	[redacted]	[redacted]	[redacted]	[redacted]
Shunt infection	[redacted]	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
End-stage renal disease	[redacted]	[redacted]	[redacted]	[redacted]
Nephrotic syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]

Post procedural haematoma	[redacted]	[redacted]	[redacted]	[redacted]
Shunt malfunction	[redacted]	[redacted]	[redacted]	[redacted]
Shunt thrombosis	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertensive urgency	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: m = number of events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants; OLP = open-label period; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event.

Notes: The column "overall" refers to overall since first dose of pegcetacoplan. 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 (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.

Source: (Sobi 2025c)

F.1 VALIANT Safety Results including OLP

A summary of common TEAEs in the RCP is provided in Table 89.

Table 89. Summary of common TEAEs (experienced by ≥3 participants in either treatment group) by SOC and PT during the RCP (Safety Set)

SoC PT	Statistics	Pegcetacoplan (n=63)	Placebo (n=61)

Any TEAE	n (%) m	[redacted]	[redacted]
Infections and infestations	n (%)	[redacted]	[redacted]
Nasopharyngitis	n (%)	[redacted]	[redacted]
Influenza	n (%)	[redacted]	[redacted]
Upper respiratory tract infection	n (%)	[redacted]	[redacted]
COVID-19	n (%)	[redacted]	[redacted]
Gastroenteritis	n (%)	[redacted]	[redacted]
Herpes zoster	n (%)	[redacted]	[redacted]
General disorders and administration site conditions	n (%)	[redacted]	[redacted]
Pyrexia	n (%)	[redacted]	[redacted]
Fatigue	n (%)	[redacted]	[redacted]
Infusion site erythema	n (%)	[redacted]	[redacted]
Injection site pruritus	n (%)	[redacted]	[redacted]
Oedema	n (%)	[redacted]	[redacted]
Oedema peripheral	n (%)	[redacted]	[redacted]
Injection site pain	n (%)	[redacted]	[redacted]
Injection site swelling	n (%)	[redacted]	[redacted]
Asthenia	n (%)	[redacted]	[redacted]
Infusion site pain	n (%)	[redacted]	[redacted]
Gastrointestinal disorders	n (%)	[redacted]	[redacted]
Nausea	n (%)	[redacted]	[redacted]
Vomiting	n (%)	[redacted]	[redacted]
Abdominal pain	n (%)	[redacted]	[redacted]
Abdominal pain upper	n (%)	[redacted]	[redacted]
Dyspepsia	n (%)	[redacted]	[redacted]

Diarrhoea	n (%)	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	n (%)	[redacted]	[redacted]
Cough	n (%)	[redacted]	[redacted]
Oropharyngeal pain	n (%)	[redacted]	[redacted]
Rhinorrhoea	n (%)	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	n (%)	[redacted]	[redacted]
Acne	n (%)	[redacted]	[redacted]
Nervous system disorders	n (%)	[redacted]	[redacted]
Headache	n (%)	[redacted]	[redacted]
Dizziness	n (%)	[redacted]	[redacted]
Injury, poisoning and procedural complications	n (%)	[redacted]	[redacted]
Contusion	n (%)	[redacted]	[redacted]
Investigations	n (%)	[redacted]	[redacted]
Blood creatine phosphokinase increased	n (%)	[redacted]	[redacted]
Blood cholesterol increased	n (%)	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	n (%)	[redacted]	[redacted]
Muscle spasms	n (%)	[redacted]	[redacted]
Renal and urinary disorders	n (%)	[redacted]	[redacted]
Acute kidney injury	n (%)	[redacted]	[redacted]
Vascular disorders	n (%)	[redacted]	[redacted]
Hypertension	n (%)	[redacted]	[redacted]
Blood and lymphatic system disorders	n (%)	[redacted]	[redacted]
Anaemia	n (%)	[redacted]	[redacted]

Note: 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 (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

Abbreviations: m, number of events; n, number of participants; PT, preferred term; RCP, randomised controlled period; SoC, system organ class; TEAE, treatment-emergent adverse event.

Source: (Sobi 2024a)

Table 90 below shows treatment-related TEAEs experienced by ≥3 participants by SOC and PT for the RCP (safety set). The most frequently reported treatment-related TEAEs (reported by ≥10% of participants) by SoC included general disorders and administration site conditions ([redacted]: [redacted]); [redacted]) and infestations ([redacted]); [redacted]). The most commonly reported treatment-related TEAEs (reported by ≥5% of participants) in either group were (pegcetacoplan vs placebo) pyrexia ([redacted]% vs [redacted]%), injection site pain ([redacted]% vs [redacted]%), and injection site swelling ([redacted]% vs [redacted]%).

Table 90. Treatment-related TEAEs (experienced by ≥3 participants) in either treatment group) by SOC and PT during the RCP (Safety Set)

SoC PT	Statistics	Pegcetacoplan (n=63) n (%)	Placebo (n=61) n (%)
Any TEAE, n (%), m	n (%)	[redacted]	[redacted]
General disorders and site conditions	n (%)	[redacted]	[redacted]
Pyrexia	n (%)	[redacted]	[redacted]
Injection site pruritus	n (%)	[redacted]	[redacted]
Injection site pain	n (%)	[redacted]	[redacted]
Injection site swelling	n (%)	[redacted]	[redacted]
Infusion site pain	n (%)	[redacted]	[redacted]
Nervous system disorders	n (%)	[redacted]	[redacted]
Headache	n (%)	[redacted]	[redacted]

Abbreviations: m, number of events; n, number of participants; PT, preferred term; RCP, randomised controlled period; SoC, system organ class; TEAE, treatment-emergent adverse event.

Source: (Sobi 2024a)

The most frequently reported TEAEs by system of organ class during the overall study (n=[redacted]) included infections and infestations (XX [XXX%], [redacted] ([redacted]); [redacted]), and [redacted] ([redacted]); these three SoCs were also the most commonly reported TEAEs during the OLP (Table 91) (Sobi 2025c).

The most frequently reported TEAEs (≥5%) by PT in both treatment groups during the OLP (n=[redacted]) included [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), and [redacted] ([redacted]). A similar profile of TEAEs (≥10%) by preferred terms (PTs) were reported during the overall study (Sobi 2025c).

Table 91. TEAEs by SoC (≥10%) and PT (≥5%) during the OLP and overall study (Safety Set)

Events by SOC and PT, n (%)	OLP			Overall (N=120)
	Pegcetacoplan-to-pegcetacoplan (n=61)	Placebo-to-pegcetacoplan (n=57)	Total (n=118)	
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]

Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]

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 all occurrences were counted in the total events count. Adverse events were coded to SOC and PT using MedDRA version 26.0.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; OLP, open-label period; PT, Preferred Term; SoC, System Organ Class; TEAE, treatment-emergent adverse event.

Source: (Sobi 2025c)

Table 92 shows treatment-related TEAEs experienced by ≥2 participants by SOC and PT during the overall study (safety set) (Sobi 2025c). SOCs without a PT meeting this threshold are not included. A treatment-related AE was defined as a TEAE with a relationship to study drug of definitely related, possibly related, or not reported.

The most frequently reported treatment-related TEAE (reported by ≥10% of participants) by SOC in the overall study included [redacted] ([redacted]). In the OLP, [redacted] ([redacted]%) participants had treatment-related TEAEs, including [redacted] ([redacted]%) participants in the pegcetacoplan-to-pegcetacoplan group and [redacted] ([redacted]%) participants in the placebo-to-pegcetacoplan group.

No treatment-related TEAEs by PT were reported by ≥5% of participants. In the overall study, the most commonly reported treatment-related TEAEs by PT were [redacted] and [redacted] ([redacted]) (Sobi 2025c).

Table 92. Treatment-related TEAEs (≥2 participants in either treatment group) by SOC and PT during the OLP and overall period (Safety Set)

Events by SOC and PT, n (%)	OLP			Overall (N=120)
	Pegcetacoplan-to-pegcetacoplan (n=61)	Placebo-to-pegcetacoplan (n=57)	Total (n=118)	
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Infusion site pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Infusion site swelling	[redacted]	[redacted]	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]

Notes: The column “overall” refers to overall since first dose of pegcetacoplan. 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 (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.

Abbreviations: m, number of events; n, number of participants; MedDRA, Medical Dictionary for Regulatory Activities; OLP, open-label period; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

Source: (Sobi 2025c)

Appendix G. Health-Related Quality of Life

G.1 Data Collection – Overview of Responses

Not applicable.

G.2 Reporting of Domains

Figure 20. EQ-5D-5L Component Score by Treatment Group and Analysis Visit for Overall Period - Component: Anxiety/Depression

Figure 21. EQ-5D-5L Component Score by Treatment Group and Analysis Visit for Overall Period - Component: Mobility

Figure 22. EQ-5D-5L Component Score by Treatment Group and Analysis Visit for Overall Period - Component: Pain/Discomfort

Figure 23. EQ-5D-5L Component Score by Treatment Group and Analysis Visit for Overall Period - Component: Self-Care

Figure 24. EQ-5D-5L Component Score by Treatment Group and Analysis Visit for Overall Period - Component: Usual Activities

G.3 Mapping

Utility values associated with CKD stages 3-5 in the model were sourced from Cooper et al. (2020), to complement the utilities for CKD stages 1 and 2 sourced from VALIANT (Section 10.3) The utilities from Cooper et al. (2020) were collected using EQ-5D-3L and estimated using UK tariff. These were mapped to Danish tariff EQ-5D-5L utilities using the algorithm presented in Torkilseng et al. (2025). The algorithm was built on patient-level data from 11 oncology trials and externally validated across three clinical trials, with the best-fitting model achieving a maximum absolute prediction error of 0.020. Prior research on similar methods indicates that such algorithms generalise well across disease areas, irrespective of the therapeutic context of the source data (Oddershede and Petersen 2015).

Using the Akaike Information Criterion for model selection, an [redacted] model was identified as the best fit, yielding the following mapping algorithm from EQ-5D-3L utility values (UK tariff) to EQ-5D-5L values (Danish tariff):

G.4 Calculation of Utility Values

Not applicable.

Appendix H. Literature Searches for the Clinical Assessment

H.1 Effect and safety of intervention and comparators

The objective of this SLR was to investigate the clinical efficacy, safety, and HRQoL of patients with C3G and primary IC-MPGN treated with pegcetacoplan.

Searches were performed on 2 September 2024 and updated on 27 May 2025. The following electronic databases were searched combining free-text terms and Medical Subject Headings (MeSH) terms for C3G and IC-MPGN and terms for comparator and intervention:

- Embase, 1974 – 27 May 2025
- MEDLINE® In-process & Other Non-indexed Citations and OVID MEDLINE, 1946 – 27 May 2025
- Cochrane library:
  - Cochrane Database of Systematic Review (CDSR)
  - Database of Abstracts of Reviews of Effects (DARE)
  - Cochrane Central Register of Controlled trials (CENTRAL)
- Cochrane Methodology Register (CMR)
  - NHS Economic Evaluations Database (NHS EED)
  - Health Technology Assessment Database (HTA)
  - American College of Physicians (ACP) journal club

Supplementary searches included searches of congress, HTA, and clinical trial registry websites. Disease terms were used to search congress websites or abstract books for the congresses detailed in Table 95. NICE, Scottish Medicines Agency (SMC), Canada's Drug Agency (CDA) and Pharmaceutical Benefits Advisory Committee (PBAC) websites were searched to identify relevant submissions. The following clinical trial registries were searched: ClinicalTrials.gov (https://clinicaltrials.gov/), World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; https://www.who.int/ictrp/en/) and European Clinical Trials Register (EU CTR; https://www.clinicaltrialsregister.eu/) (Table 94).

Table 93. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 to 23 May 2025	27.05.2025

Medline	pubmed.ncbi.nlm.nih.gov	1946 to 23 May 2025	27.05.2025
CENTRAL	Cochrane library	April 2025	27.05.2025
CDSR	Cochrane library	2005 to 21 May 2025	27.05.2025
DARE	Cochrane library	1991 to April 2025	27.05.2025
CMR	Cochrane library	1991 to April 2025	27.05.2025
NHS EED	Cochrane library	1991 to April 2025	27.05.2025
HTA	Cochrane library	1991 to April 2025	27.05.2025
ACP	Cochrane library	1991 to April 2025	27.05.2025

Abbreviations: ACP, American College of Physicians; CDSR, Cochrane Database of Systematic Review; CENTRAL, Cochrane Central Register of Controlled trials; CMR, Cochrane Methodology Register; DARE, Database of Abstracts of Reviews of Effects; HTA, Health Technology Assessment Database; NHS EED, NHS Economic Evaluations Database

Table 94. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	03.06.2025
CDA	www.cda-amc.ca	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	03.06.2025
SMC	www.scottishmedicines.org.uk/	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex	03.06.2025

		membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	
PBAC	www.pbs.gov.au	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	03.06.2025
Clinicaltrials.gov	www.clinicaltrials.gov	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	04.06.2025
WHO ICTRP	www.who.int/ictrp/en	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	04.06.2025
EU CTR	www.clinicaltrialsregister.eu	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	04.06.2025

Abbreviations: CDA, Canada's Drug Agency; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform

Table 95. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Nephrology (ASN)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	03.06.2025
European Renal Association (ERA)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	20.06.2025
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	03.06.2025
UK Kidney Week	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	17.06.2025
World Congress of Nephrology (WCN)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	27.05.2025

H.1.1 Search Strategies

Table 96, Table 97, and Table 98 present the search strategies for Embase, MEDLINE, and Cochraine performed on 27 May 2025. In each search strategy, query #4 was only applied in the May 2025 update. All other queries align between the original SLR and the SLR update.

Table 96. Search strategy table for Embase

No.	Query	Results
#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.	22 795
#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
#3	1 and 2	119
#4	limit 3 to yr="2024 -Current"	46

Table 97. Search strategy table for MEDLINE

No.	Query	Results
#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
#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
#3	1 and 2	16

#4	limit 3 to yr="2024 -Current"	11

Table 98. Search strategy table for Cochrane

No.	Query	Results
#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
#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
#3	1 and 2	47
#4	limit 3 to yr="2024 -Current"	14

H.2 Systematic Selection of Studies and References

The research question contains elements that need to be defined before the start of the evidence collection. These include population, interventions, comparators, outcomes, and study design (PICOS) (Table 99).

To meet the objectives of this review, articles identified by the searches were assessed against the eligibility criteria presented in Table 99. References from the database searches were deduplicated, and the titles and abstracts of articles were double-blind screened by two independent reviewers using Rayyan (Ouzzani et al. 2016), a web-based tool designed to aid the screening process of SLRs, to determine whether articles meet the predefined eligibility criteria (Table 99). Supplementary searches were performed, and articles were also screened against eligibility criteria.

Full texts were obtained for articles meeting the inclusion criteria or where the eligibility was unclear and double-blind review by two independent reviewers confirmed eligibility. Remaining uncertainties were resolved by discussion with a third reviewer.

The data from relevant articles were extracted by a single reviewer for a predetermined range of variables. Data were checked and validated by a second reviewer.

Table 99. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
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	
Intervention	Pegcetacoplan (Aspaveli, Empaveli, Syfovre, APL-2)		
Comparators	• Iptacopan (Fabhalta, LNP023) • ARO-C3 • SAR443809 • BCX10013 • ADX-097 • KP104 • NM8074 • Zaltenibart (OMS906)		
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	• Outcomes not relating to economic evaluations, resource use, and utilities • PK/PD outcomes	

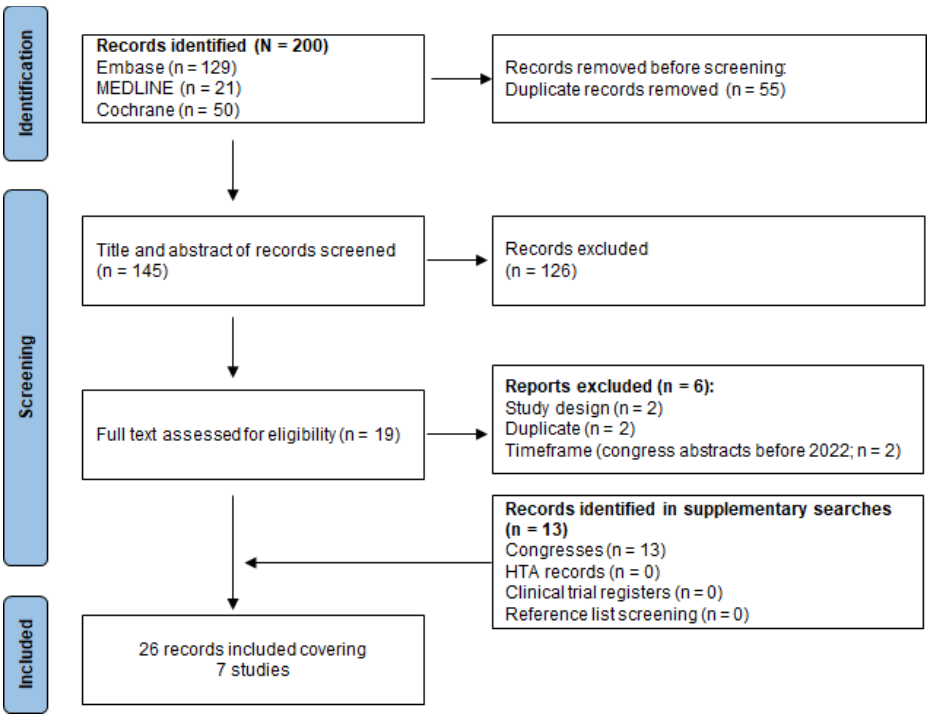
	Safety and tolerability, including but not limited to: • any grade 3/4 AEs • any SAEs • discontinuation due to AEs • AESI Any HRQoL or PRO outcomes (e.g. reported from EQ-5D, SF-36, FACIT-fatigue, KDQoL, PGCI scale)	
Study design/publication type	• RCTs • Interventional non-RCTs: • non-randomised comparative studies • single-arm clinical trials ○ other prospective, interventional studies, including single-arm trials • Full-text publications • Congress abstracts	• Observational, RWE studies • Case reports, case series • Systematic and narrative reviews[a]
Language restrictions	No limits	

[a]Bibliographies of relevant systematic reviews and meta-analysis will be screened for studies of interest.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; 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 of Life Instrument; 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; uPCR, urine protein/creatinine ratio.

The electronic searches were performed on 2 September 2024 and updated on 27 May 2025. Across both the original and updated searches, following de-duplication, 145 articles were screened for inclusion. In total, 126 articles were excluded at the screening stage and six at the full-text review stage. Thirteen relevant congress abstracts were identified from supplementary searches. Twenty-six articles, reporting on seven studies, met the eligibility criteria and were included in this SLR (Figure 25).

Figure 25. PRISMA flow diagram - clinical SLR



Of the seven studies included, three reported on pegcetacoplan (Bomback et al. 2024a, Bomback et al. 2023, Fakhouri et al. 2024, Quintana-Gallardo et al. 2024, Dixon et al. 2023).

Clinical studies that investigated pegcetacoplan:

- NOBLE (NCT04572854) was a multinational, prospective, phase 2 RCT investigating the efficacy and safety of 12 weeks of pegcetacoplan (n=10) or 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 (Bomback et al. 2025b), as well as five congress materials (Bomback et al. 2024a, Bomback et al. 2023, Fakhouri et al. 2024, Quintana-Gallardo et al. 2024, Java et al. 2024) including *post hoc* analyses of patient-level data (Fakhouri et al. 2024) and patient evolution through to 52 weeks that included a 40-week pegcetacoplan open-label treatment period after the initial comparative 12-week period (Java et al. 2024).
- DISCOVERY (NCT03453619) was a single-arm, open-label, phase 2 study conducted in the USA investigating the efficacy and safety of 48 weeks of pegcetacoplan in eight adult or adolescent patients with native C3G, and its findings have been reported in a peer-reviewed journal (Dixon et al. 2023).
- 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.(Fakhouri et al. 2025a, Gale et al. 2025, Oosterveld et al. 2025, Kavanagh D 2025, Mastrangelo et al. 2025, Nester et al. 2025a, Vivarelli et al. 2025a, Vivarelli et al. 2025b) The study is reported in

eight congress materials, including posters, presentations, and abstracts. The reports include efficacy and safety analysis of up to 52 weeks (Fakhouri et al. 2025a), subgroup analyses of adolescent population (Mastrangelo et al. 2025, Vivarelli et al. 2025a) and patients with disease recurrence (Oosterveld et al. 2025), as well as *post hoc* analyses of patients with nephrotic-range proteinuria (Vivarelli et al. 2025b) and concomitant immunosuppression (Kavanagh D 2025).

A compilation of included references is provided in Table 101.

Table 100. Studies/references included in the Danish assessment

Study	Reference(s)
VALIANT NCT05067127	Fakhouri F, Bomback AS, Ariceta G, Delmas Y, Dixon BP, Gale DP, Greenbaum LA, Han SH, Isbel N, Le Quintrec M, Licht C, Mastrangelo A, Mizuno M, Neves de Holanda MI, Pickering MC, Remuzzi G, Van De Kar N, Vivarelli M, Walker PD, Wallace D, Zecher D, Francois C, Deschatelets P, Li L, Wang Z, Abad-Franch L, Kinnman N, López-Lázaro L, Szamosi J, Nester CM; VALIANT Trial Investigators Group. Trial of Pegcetacoplan in C3 Glomerulopathy and Immune-Complex MPGN. N Engl J Med. 2025 Dec 4;393(22):2210-2220. doi: 10.1056/NEJMoa2501510.

Table 101. List of included references in the clinical SLR

Author	Title	Year
Dixon, B. P. and Greenbaum, L. A. and Huang, L. and Rajan, S. and Ke, C. and Zhang, Y. and Li, L.	Clinical Safety and Efficacy of Pegcetacoplan in a Phase 2 Study of Patients with C3 Glomerulopathy and Other Complement-Mediated Glomerular Diseases	2023
Bomback, A. S. and Daina, E. and Kanellis, J. and Kavanagh, D. and Pickering, M. C. and Sunder-Plassmann, G. and Walker, P. D. and Wang, Z. and Ahmad, Z. and Fakhouri, F.	Efficacy of 12-Week Pegcetacoplan in Kidney Transplant Recipients with Recurrent C3 Glomerulopathy (C3G) or Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN)	2023
Bomback, A. S. and Daina, E. and Kanellis, J. and Kavanagh, D. and Pickering, M. C. and Sunder-Plassmann, G. and Walker, P.	Efficacy of 12-week pegcetacoplan in kidney transplant recipients with recurrent C3 glomerulopathy (C3G) or	2024

D. and Wang, Z. and Ahmad, Z. and Fakhouri, F.	immune complex membranoproliferative glomerulonephritis (IC-MPGN)	
Quintana-Gallardo, L. and Bomback, A. and Daina, E. and Kanellis, J. and Kavanagh, D. and Pickering, M. C. and Sunder-Plassmann, G. and Walker, P. and Wang, Z. and Ahmad, Z. and Fakhouri, F.	Wcn24-683 Efficacy of 12-Week Pegcetacoplan in Kidney Transplant Recipients with Recurrent C3 Glomerulopathy (C3G) or Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN)	2024
Fakhouri F, Bomback A, Kavanagh D, Remuzzi G, Sunder-Plassmann G, Kanellis J, Daina E, Walker P, Wang Z and Ahmad Z	Pegcetacoplan for post-transplant recurrent C3 glomerulopathy or immune complex membranoproliferative glomerulonephritis in NOBLE: 12-week evolution	2024
Bomback, A. S. and Daina, E. and Remuzzi, G. and Kanellis, J. and Kavanagh, D. and Pickering, M. C. and Sunder-Plassmann, G. and Walker, P. D. and Wang, Z. and Ahmad, Z. and Fakhouri, F.	Efficacy and Safety of Pegcetacoplan in Kidney Transplant Recipients With Recurrent Complement 3 Glomerulopathy or Primary Immune Complex Membranoproliferative Glomerulonephritis	2025
Java, A. and Bomback, A. S. and Kavanagh, D. and Remuzzi, G. and Sunder-Plassmann, G. and Kanellis, J. and Daina, E. and Walker, P. D. and Wang, Z. and Ahmad, Z. and Fakhouri, F.	Pegcetacoplan for Post-transplant Recurrent C3 Glomerulopathy (C3G) or Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN) in NOBLE: 52-Week Patient Evolution	2024
Nester, C. and Bomback, A. and Iraola, M. A. G. A. and Delmas, Y. and Dixon, B. P. and Gale, D. and Greenbaum, L. and Han, S. H. and Isbel, N. and Licht, C. and Mastrangelo, A. and Mizuno, M. and Neves De Holanda, M. I. and Pickering, M. C. and Remuzzi, G. and Van De Kar, N. and Vivarelli, M. and Walker, P. and Wallace, D. and Zecher, D. and Li, L. and Wang, Z. and Lopez Lazaro, L. and Szamosi, J. and Fakhouri, F.	VALIANT: Randomized, multicenter, double-blind, placebo controlled, phase 3 trial of pegcetacoplan for patients with native or posttransplant recurrent C3G or primary IC-MPGN	2025
Vivarelli, M. and Ariceta, G. and Borovitz, Y. and Dixon, B. P. and Greenbaum, L. and Licht, C. and Mastrangelo, A. and Melhem, N. and Fujita, N. and Van De Kar, N. and Wallace, D. and Li, L. and Lopez Lazaro, L. and Szamosi, J. and Nester, C. and Zecher, D.	Pegcetacoplan for adolescents with complement 3 glomerulopathy or primary immune complex-membranoproliferative glomerulonephritis: VALIANT phase 3 double-blind placebo-controlled trial subgroup analysis	2025
Vivarelli M, Bomback AS, Ariceta G, Mastrangelo A, Nester CM, Remuzzi G, Van De Kar N, Wang Z, Szamosi J, Decker D, Quintana-Gallardo L, Fakhouri F	Pegcetacoplan Treatment Effect in Patients With Nephrotic Range Proteinuria: Results From the VALIANT	2025

	Phase 3 Study in Patients With C3G or Primary (Idiopathic) IC-MPGN	
Kavanagh D, Bomback AS, Ariceta G, Mastrangelo A, Nester CM, Remuzzi G, Vivarelli M, Wang Z, Szamosi J, Decker D, Quintana-Gallardo L, Fakhouri F	Pegcetacoplan Demonstrates Clinically Significant Responses in C3G and Primary (Idiopathic) IC-MPGN Patients With or Without Concomitant Immunosuppression in VALIANT	2025
Mastrangelo A, Vivarelli M, Ariceta G, Borovitz Y, Dixon BP, Licht C, Melhem N, Van De Kar N, Wallace D, Li L, Lopez Lazaro L, Nester CM	Targeted Treatment With Pegcetacoplan for Adolescents With C3G or Primary (Idiopathic) IC-MPGN in the VALIANT Phase 3 Trial	2025
Js Oosterveld M, Kaufeld J, Zecher D, Claes K, Zuber J, Noronha IL, Bomback AS, Wang Z, Szamosi J, Li L, Lopez-Lazaro L, Viklicky O	Targeted Treatment With Pegcetacoplan for Post-Transplant Recurrent C3G or Primary (idiopathic) IC-MPGN in the VALIANT Phase 3 Trial	2025
Gale DP, Bomback AS, Licht C, Nester CM, Pickering MC, Remuzzi G, Van De Kar N, Wang Z, Szamosi J, Decker D, Quintana Gallardo L, Fakhouri F	Pegcetacoplan Treatment Appears to Halt Disease Progression in C3G and Primary (Idiopathic) IC-MPGN Patients: Results from the Phase 3 VALIANT Study	2025
Fakhouri F, Ariceta G, Bomback AS, Dixon BP, LeQuintrecM, Mastrangelo A, Pickering MC, Remuzzi G, Van De Kar N, Vivarelli M, Zecher D, Nester CM	Pegcetacoplan for C3G and primary (idiopathic) IC-MPGN: 52 -week results from the phase 3 VALIANT trial show sustained efficacy	2025
Wong, E. and Nester, C. and Cavero, T. and Karras, A. and Le Quintrec, M. and Lightstone, L. and Eisenberger, U. and Soler, M. J. and Kavanagh, D. and Daina, E. and Praga, M. and Medjeral-Thomas, N. R. and Gackler, A. and Garcia-Carro, C. and Biondani, A. and Chaperon, F. and Kulmatycki, K. and Milojevic, J. and Webb, N. J. A. and Nidamarthy, P. K. and Junge, G. and Remuzzi, G.	Efficacy and Safety of Iptacopan in Patients With C3 Glomerulopathy	2023
Nester, C. M. and Eisenberger, U. and Karras, A. and le Quintrec, M. and Lightstone, L. and Praga, M. and Remuzzi, G. and Soler, M. J. and Liu, J. and Meier, M. and Tawfik, R. and Junge, G. and Biondani, A. and Trapani, A. J. and Webb, N. J. A. and Wong, E. K. S.	Iptacopan Reduces Proteinuria and Stabilizes Kidney Function in C3 Glomerulopathy	2025
Nester, C. M. and Eisenberger, U. and Karras, A. and le Quintrec-Donnette, M. and Lightstone, L. and Praga, M. and Remuzzi, G. and Jose Soler, M. and Liu, J. and Meier, M. and Tawfik, R. and Junge,	Wcn23-0403 an Open-Label, Non-Randomized Extension Study to Evaluate Long-Term Efficacy, Safety, and Tolerability of Lnp023 in Subjects with C3	2023

G. and Biondani, A. and A, J. Trapani and Webb, N. and E, K. Wong	Glomerulopathy: Interim Analysis of Phase 2 Study	
Nester, C. M. and Eisenberger, U. and Karras, A. and Lightstone, L. and Praga, M. and Remuzzi, G. and Jose Soler, M. and Liu, J. and Meier, M. and Tawfik, R. and Junge, G. and Biondani, A. and Trapani, A. J. and Webb, N. and Wong, E. K.	12M Interim Analysis of an Open-Label, Non-Randomized Extension of a Phase 2 Study to Evaluate the Long-Term Efficacy, Safety, and Tolerability of Iptacopan in Subjects With C3G	2022
Meier, M.	An open-label, non-randomized extension study to evaluate the long-term efficacy, safety and tolerability of LNP023 in subjects with C3 glomerulopathy: Interim analysis of a Phase 2 study	2022
Nester CM, Eisenberger U, Karras A, Le Quintrec M, Lightstone L, Praga M, Remuzzi G, José Soler Romeo M, Liu J, Meier M, Webb N and Wong E	Update to the long-term safety and efficacy of iptacopan in C3G: 33-month extension study data from patients enrolled in a phase 2 study	2024
Nester, C. and Smith, R. and Kavanagh, D. and Vivarelli, M. and Remuzzi, G. and Zhao, M. H. and Wong, E. and Wang, Y. and Trapani, A. and Krishnan, I. and Webb, N. and Meier, M. and Bomback, A.	Efficacy and Safety of Iptacopan in Patients with C3 Glomerulopathy: 12-Month Results from the Phase 3 Appear-C3G Study	2025
Caravaca-Fontan F, Zhao M, Smith R, Israni R, Wang Y, Liu J, Smeets S, Keefe D	Reduction of hematuria and albuminuria with iptacopan in C3G: Findings from APPEARC3G study	2025
Daina E, Remuzzi G, Kavanagh D, Schuhmann I, Israni R, Kalluri H, Keefe D, Wang Y, Liu J, De Vries A	Iptacopan's rapid and sustained inhibition of overactive complement alternative pathway in C3G: Exploratory analysis from the Phase 3 APPEAR-C3G study	2025
Weinmann-Menke J, Java A, Kalluri H, Keefe D, Ansari S, Liu J, Smeets S, Bomback A	Evaluation of C3 deposition in patients with C3G: insights from the APPEAR-C3G Phase 3 study in patients treated with iptacopan	2025
Kavanagh D, Licht C, Smeets S, Israni R, Keefe D, Ansari S, Liu J, Nester CM	Long-term stabilization of kidney function (estimated glomerular filtration rate) with iptacopan in patients with native C3 glomerulopathy	2025

A list of excluded full-text references is provided in Table 102.

Table 102. Excluded studies/references

Study	Reason
Dixon BP, Greenbaum LA, Huang L et al. C3 inhibition with pegcetacoplan targets the underlying disease process of C3 glomerulopathy (C3G) and improves proteinuria. Journal of the American Society of Nephrology 2020;Conference: Kidney Week 2020. Virtual United States. 31:577.	Congress abstract out of date scope
Wong EKS, Praga M, Nester C et al. Iptacopan (LNP023): A novel oral complement alternative pathway factor B inhibitor safely and effectively stabilises EGFR in C3 glomerulopathy. Nephrology Dialysis Transplantation 2021;36(SUPPL 1):i25.	Congress abstract out of date scope
Memon, M. F. and Hussain, S. I. and Memon, Z. F. and Memon, S. F. Selective factor B inhibition with iptacopan: transforming C3 glomerulopathy management. International Urology and Nephrology 2025.	Study design
Nester, C. and Eisenberger, U. and Karras, A. and Le Quintrec, M. and Lightstone, L. and Praga, M. and Remuzzi, G. and Soler, M. J. and Liu, J. and Meier, M. and Webb, N. J. and Wong, E. K. Update to the Long-Term Safety and Efficacy of Iptacopan in C3g: 33-Month Extension Study Data from Patients Enrolled in a Phase 2 Study. Kidney International Reports 2025; 10:S618.	Duplicate
Nester, C. M. and Smith, R. J. and Kavanagh, D. and Vivarelli, M. and Remuzzi, G. and Zhao, M. H. and Wong, E. K. and Wang, Y. and Trapani, A. J. and Krishnan, I. and Webb, N. J. and Meier, M. and Bomback, A. S. Efficacy and Safety of Iptacopan in Patients with C3 Glomerulopathy: 12-Month Results from the Phase 3 APPEAR-C3G Study. Journal of the American Society of Nephrology 2024; 86.	Duplicate
Smeets, S. and Ansari, S. and Rizk, S. and Krishnan, I. and Webb, N. J. and Meier, M. Experience with Iptacopan in Patients with Recurrent Complement 3 Glomerulopathy (C3G): Early Access Program Data. Journal of the American Society of Nephrology 2024; :1079.	Study design

Appendix I. Literature Searches for Health-Related Quality of Life

I.1 Systematic Search

A SLR was conducted to investigate the economic outcomes of treatment of patients with C3G and primary IC-MPGN, including economic evaluations, costs, health care resource utilisation (HCRU) and utilities.

For further information, see Appendix J.

Table 103. Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 to 30 August 2024	02.07.2025
Medline	pubmed.ncbi.nlm.nih.gov	1946 to 29 August 2025	02.07.2025
CENTRAL	Cochrane library	July 2024	02.07.2025
CDSR	Cochrane library	2005 to 28 August 2024	02.07.2025
DARE	Cochrane library	1991 to August 2024	02.07.2025
CMR	Cochrane library	1991 to August 2024	02.07.2025
NHS EED	Cochrane library	1991 to August 2024	02.07.2025
HTA	Cochrane library	1991 to August 2024	02.07.2025
ACP	Cochrane library	1991 to August 2024	02.07.2025

Abbreviations: ACP, American College of Physicians; CDSR, Cochrane Database of Systematic Review; CENTRAL, Cochrane Central Register of Controlled trials; CMR, Cochrane Methodology Register; DARE, Database of Abstracts of Reviews of Effects; HTA, Health Technology Assessment Database; NHS EED, NHS Economic Evaluations Database

Table 104. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis,	07.07.2025

		membranoproliferative glomerulonephritis, MPGN	
CDA	www.cda-amc.ca	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
PBAC	www.pbs.gov.au	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
SMC	www.scottishmedicines.org.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
Cost-Effectiveness Analysis (CEA) registry	www.cevr.tuftsmedicalcenter.org/databases/cea-registry	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
EuroQoL	www.euroqol.org	C3 glomerulopathy, C3G, C3	07.07.2025

		glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	
Research Papers in Economics	www.repec.org/	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	08.07.2025
MAPI institute	www.mapi-institute.com	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
National Institute for Health Research HTA	www.nihr.ac.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
International Network of Agencies for HTA	www.inahta.org	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis,	07.07.2025

		membranoproliferative glomerulonephritis, MPGN	
University of Sheffield ScHARRHUD utility database	scharr-outcomes.sites.sheffield.ac.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
Institute for Clinical and Economic Review	www.icer.org/explore-our-research	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025

Abbreviations: CDA, Canada's Drug Agency; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Agency; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform

Table 105. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Nephrology (ASN)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025
European Renal Association (ERA)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025
UK Kidney Week	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025
World Congress of Nephrology (WCN)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025

I.1.1 Search Strategies

Table 106, Table 107 and Table 108 present the search strategies for Embase, MEDLINE, and Cochraine performed on 02 July 2025.

Table 106. Search strategy table for Embase

No.	Search	Hits
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.	23 069
2	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp.	3 014 982

	or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health care financing/ or health economics.mp. or health economics/ or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or health care planning/ or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	
3	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	452 754
4	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	182 117
5	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	39 669
6	quality of life/ and ec.fs.	73 766
7	quality of life/ and (health adj3 status).ti,ab,kw.	24 926
8	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	7648
9	or/2-8	3 305 595
10	1 and 9	2577
11	(animal$ not human$).sh,hw.	5 130 913
12	10 not 11	2556
13	limit 12 to yr=“2024-current”	221

Table 107. Search strategy table for MEDLINE

No.	Search	Hits
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.	13 817
2	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health care financing/ or health economics.mp. or health economics/ or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or health care planning/ or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	1 793 016
3	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	286 862
4	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty	109 664

	six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	
5	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	17 990
6	quality of life/ and ec.fs.	11 451
7	quality of life/ and (health adj3 status).ti,ab,kw.	12 990
8	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	19 074
9	or/2-8	1 955 551
10	1 and 9	934
11	(animal$ not human$).sh,hw.	5 307 493
12	10 not 11	908
13	limit 12 to yr="2024-current"	92

Table 108. Search strategy table for Cochraine

No.	Search	Hits
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.	983
2	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health care financing/ or health economics.mp. or health economics/ or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or health care planning/ or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp.	195 557

	or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	
3	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	61 490
4	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	45 314
5	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	3806
6	quality of life/ and ec.fs.	3328
7	quality of life/ and (health adj3 status).ti,ab,kw.	2219
8	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	5037
9	or/2-8	230 503
10	1 and 9	180
11	(animal$ not human$).sh,hw.	3497
12	10 not 11	180
13	limit 12 to yr="2024-current"	10

Relevance of all identified articles was decided by reviewing against the eligibility criteria in Table 109.

Results from the database searches were deduplicated and the titles and abstracts of articles were screened by two independent reviewers using Rayyan (Ouzzani et al. 2016), a web-based tool designed to aid the screening process of SLRs, to determine whether articles meet the predefined eligibility criteria. Supplementary searches were performed and articles were also screened against eligibility criteria.

Full texts of articles meeting the inclusion criteria or articles in which the eligibility was unclear were obtained and reviewed by two independent reviewers (performed retrospectively in the original search) to confirm eligibility. No additional criteria were added during the study selection process.

The data from relevant articles were extracted by a single reviewer for a predetermined range of variables, including study details, outcome measures of interest, and key findings. Data were checked and validated by a second reviewer.

Table 109. Eligibility criteria for the HRQoL SLR

Description	Inclusion criteria	Exclusion criteria
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
Intervention	Any	
Comparators	Any	

Outcomes	**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
	
	Costs and resource use associated with treatment and complications
	• 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)
		• Outcomes not relating to economic evaluations, resource use, costs and QoL/utilities

	• Social impact (direct and indirect non-medical costs)	

	QoL/utilities
	• Studies reporting utilities and disutilities for the population of interest using any utility measure, including (but not limited to) the following:
	  ○ EQ-5D (3L or 5L)
	  ○ HUI
	  ○ SF-6D
	  ○ SF-36
	  ○ standard gamble
	• time trade off	

Study design	• Any study type, including economic models and evaluations	• Animal/*in vitro* studies • Case reports, case series • Systematic and narrative reviews[a]
Article type	• Full-text publications • Congress abstracts	• Review, editorial, letter, protocol-only publications
Language	No limits	
Country restrictions	None	
Date restrictions	• Full publications: 2014 to present • For congress abstracts, 2022 to present	• Before 2014 for full publications • Before 2022 for congress abstracts

[a]Bibliographies of relevant systematic reviews and meta-analysis were screened for studies of interest.

Abbreviations: C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; EQ-5D, EuroQol Five-Dimension questionnaire; HUI, Health Utility Index; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; QALY, quality-adjusted life years; QoL, quality of life; SF-36, 36-

item Short-form Health Survey; SF-6D, Short-Form Six-Dimension; SLR, systematic literature review; WPAI, Work Productivity and Activity Impairment Questionnaire.

I.1.2 Results

See Appendix J.1.2 for results and the PRISMA flow diagram.

Evidence on the patient burden and impact on HRQoL and utilities for patients with C3G and primary IC-MPGN was scarce: only three articles reported on HRQoL using a generic patient-reported outcome instrument (Lafayette et al. 2024b, Sidhu et al. 2024, Rich et al. 2024) (Table 110).

Table 110. Results of the HRQoL SLR

Title	Author	Year
Quality of life and fatigue burden in individuals living with complement 3 glomerulopathy – a real-world study	Lafayette R, Sidhu R, Proudfoot C *et al.*	2024
Self-reported quality of life in complement 3 glomerulopathy patients delineated by CKD stage: a real-world, multi-country survey	Sidhu R, Proudfoot C, Pannagl K *et al.*	2024
Real-world survey on healthcare resource utilisation and physician-reported burden in patients with primary Immune Complex Membranoproliferative Glomerulonephritis	Carly Rich, Dima Decker, Lucía Quintana-Gallardo, James Jackson, Sarah Clayton, Kristie Fitzmaurice, Mollie Lowe, Katie Gordon, Mingyi Huang	2024

I.2 Focused Search

No targeted literature search was performed to inform HRQoL.

Appendix J. Literature Searches for Additional Inputs to the Health Economic Model

J.1 Systematic Search

A SLR was conducted to investigate the economic outcomes of treatment of patients with C3G and primary IC-MPGN, including economic evaluations, costs, HCRU, and utilities.

Searches were performed on 2 September 2024 and updated on 2 July 2025. The following electronic databases were searched combining free-text terms and MeSH terms for C3G and IC-MPGN and terms for outcomes of interest:

- Embase, 1974 – 2 July 2025
- MEDLINE® In-process & Other Non-indexed Citations and OVID MEDLINE, 1946 – 2 July 2025
- Cochrane library:
    - Cochrane Database of Systematic Review (CDSR)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Cochrane Central Register of Controlled trials (CENTRAL)
- Cochrane Methodology Register (CMR)
    - NHS Economic Evaluations Database (NHS EED)
    - Health Technology Assessment Database (HTA)
    - American College of Physicians (ACP) journal club.

Date limitations were applied to the searches: journal publications were restricted to 2014 to present and congress abstracts restricted to 2022 to present. Any study design was included if presented outcomes relating to economic evaluations, costs and resource use, or utilities. Systematic and narrative reviews were excluded but the reference lists of relevant reviews were screened for original publications. The search strings used to identify evidence are listed in Table 114, Table 115 and Table 116.

Supplementary searches included congress hand searches, HTA website searches and additional grey literature searches (Table 112). The conferences searched are detailed in Table 113.

The following HTA websites were also searched:

- NICE

- Scottish Medicines Agency (SMC)
- Canada's Drug Agency (CDA)
- Pharmaceutical Benefits Advisory Committee (PBAC).

Finally, the following grey literature sources were searched:

- Cost-Effectiveness Analysis (CEA) registry (https://cevr.tuftsmedicalcenter.org/databases/cea-registry)
- EuroQoL website
- Research Papers in Economics (RePEc; http://repec.org/)
- MAPI Institute
- National Institute for Health Research HTA
- International Network of Agencies for HTA
- University of Sheffield ScHARRHUD utility database
- Institute for Clinical and Economic Review (ICER; https://icer.org/explore-our-research/).

Table 111. Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 to 30 August 2024	02.07.2025
Medline	pubmed.ncbi.nlm.nih.gov	1946 to 29 August 2025	02.07.2025
CENTRAL	Cochrane library	July 2024	02.07.2025
CDSR	Cochrane library	2005 to 28 August 2024	02.07.2025
DARE	Cochrane library	1991 to August 2024	02.07.2025
CMR	Cochrane library	1991 to August 2024	02.07.2025
NHS EED	Cochrane library	1991 to August 2024	02.07.2025
HTA	Cochrane library	1991 to August 2024	02.07.2025
ACP	Cochrane library	1991 to August 2024	02.07.2025

Abbreviations: ACP, American College of Physicians; CDSR, Cochrane Database of Systematic Review; CENTRAL, Cochrane Central Register of Controlled trials; CMR, Cochrane Methodology Register; DARE, Database of Abstracts of Reviews of Effects; HTA, Health Technology Assessment Database; NHS EED, NHS Economic Evaluations Database

Table 112. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

NICE	www.nice.org.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
CDA	www.cda-amc.ca	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
PBAC	www.pbs.gov.au	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
SMC	www.scottishmedicines.org.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
Cost-Effectiveness Analysis (CEA) registry	www.cevr.tuftsmedicalcenter.org/databases/cea-registry	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN,	07.07.2025

		immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	
EuroQoL	www.euroqol.org	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
Research Papers in Economics	www.repec.org/	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	08.07.2025
MAPI institute	www.mapi-institute.com	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
National Institute for Health Research HTA	www.nihr.ac.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative	07.07.2025

		glomerulonephritis, MPGN	
International Network of Agencies for HTA	www.inahta.org	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
University of Sheffield ScHARRHUD utility database	scharr-outcomes.sites.sheffield.ac.uk	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025
Institute for Clinical and Economic Review	www.icer.org/explore-our-research	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis, MPGN	07.07.2025

Abbreviations: CDA, Canada's Drug Agency; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Agency; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform

Table 113. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Nephrology (ASN)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex	07.07.2025

			membranoproliferative glomerulonephritis	
European Renal Association (ERA)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025
UK Kidney Week	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025
World Congress of Nephrology (WCN)	conference website	Skimming through abstract collection	C3 glomerulopathy, C3G, C3 glomerulonephritis, DDD, dense deposit disease, IC-MPGN, immune complex membranoproliferative glomerulonephritis	07.07.2025

J.1.1 Search Strategies

Table 114, Table 115 and Table 116 present the search strategies for Embase, MEDLINE, and Cochrane performed on 02 July 2025.

Table 114. Search strategy table for Embase

No.	Search	Hits
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-	23 069

	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	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health care financing/ or health economics.mp. or health economics/ or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or health care planning/ or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	3 014 982
3	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	452 754
4	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	182 117
5	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	39 669
6	quality of life/ and ec.fs.	73 766
7	quality of life/ and (health adj3 status).ti,ab,kw.	24 926

8	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	7648
9	or/2-8	3 305 595
10	1 and 9	2577
11	(animal$ not human$).sh,hw.	5 130 913
12	10 not 11	2556
13	limit 12 to yr="2024-current"	221

Table 115. Search strategy table for MEDLINE

No.	Search	Hits
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.	13 817
2	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health care financing/ or health economics.mp. or health economics/ or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or health care planning/ or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	1 793 016
3	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	286 862

4	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	109 664
5	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	17 990
6	quality of life/ and ec.fs.	11 451
7	quality of life/ and (health adj3 status).ti,ab,kw.	12 990
8	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	19 074
9	or/2-8	1 955 551
10	1 and 9	934
11	(animal$ not human$).sh,hw.	5 307 493
12	10 not 11	908
13	limit 12 to yr=“2024-current”	92

Table 116. Search strategy table for Cochraine

No.	Search	Hits
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.	983
2	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver	195 557

	burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health care financing/ or health economics.mp. or health economics/ or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or health care planning/ or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	
3	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	61 490
4	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	45 314
5	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	3806
6	quality of life/ and ec.fs.	3328
7	quality of life/ and (health adj3 status).ti,ab,kw.	2219
8	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	5037
9	or/2-8	230 503
10	1 and 9	180
11	(animal$ not human$).sh,hw.	3497
12	10 not 11	180
13	limit 12 to yr="2024-current"	10

Relevance of all identified articles was decided by reviewing against the eligibility criteria in Table 117.

Results from the database searches were deduplicated and the titles and abstracts of articles were screened by two independent reviewers using Rayyan (Ouzzani et al. 2016a), a web-based tool designed to aid the screening process of SLRs, to determine whether articles meet the predefined eligibility criteria. Supplementary searches were performed and articles were also screened against eligibility criteria.

Full texts of articles meeting the inclusion criteria or articles in which the eligibility was unclear were obtained and reviewed by two independent reviewers (performed retrospectively in the original search) to confirm eligibility. No additional criteria were added during the study selection process.

The data from relevant articles were extracted by a single reviewer for a predetermined range of variables, including study details, outcome measures of interest, and key findings. Data were checked and validated by a second reviewer.

Table 117. Eligibility criteria for the economic SLR

Description	Inclusion criteria	Exclusion criteria
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
Intervention	Any	
Comparators	Any	
Outcomes	**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

	Costs and resource use associated with treatment and complications • 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)	

	QoL/utilities
	• Studies reporting utilities and disutilities for the population of interest using any utility measure, including (but not limited to) the following:
	  ○ EQ-5D (3L or 5L)
	  ○ HUI
	  ○ SF-6D
	  ○ SF-36
	  ○ standard gamble
	• time trade off	

Study design	• Any study type, including economic models, and evaluations	• Animal/*in vitro* studies • Case reports, case series • Systematic and narrative reviews[a]
Article type	• Full-text publications • Congress abstracts	• Review, editorial, letter, protocol-only publications
Language	No limits	
Country restrictions	None	
Date restrictions	• Full publications: 2014 to present • For congress abstracts, 2022 to present	• Before 2014 for full publications

- Before 2022 for congress abstracts

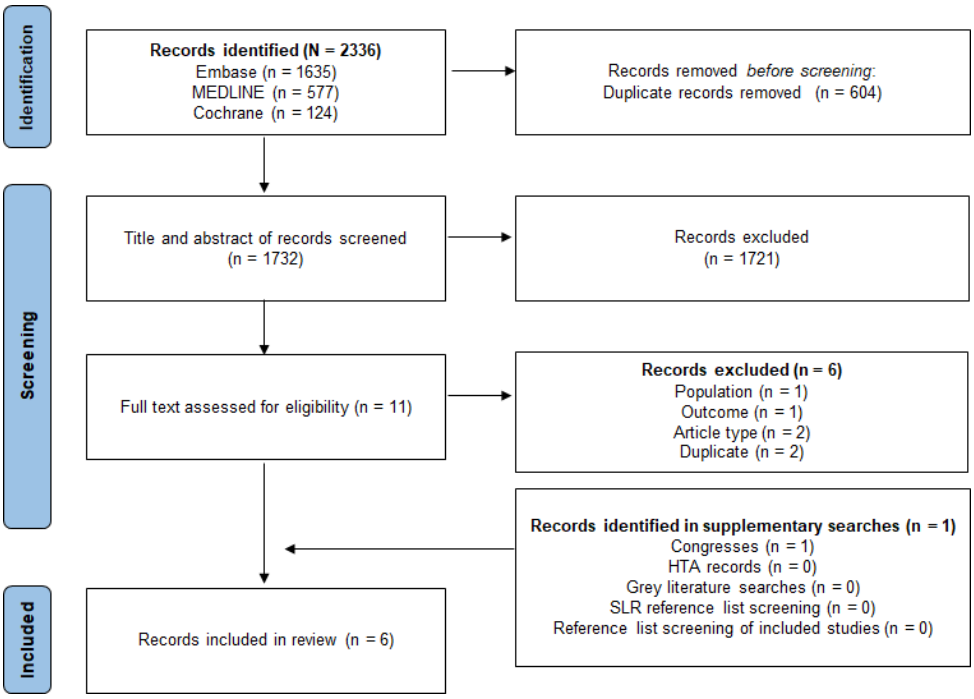
[a]Bibliographies of relevant systematic reviews and meta-analysis were screened for studies of interest.

Abbreviations: C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; EQ-5D, EuroQol Five-Dimension questionnaire; HUI, Health Utility Index; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; QALY, quality-adjusted life years; QoL, quality of life; SF-36, 36-item Short-form Health Survey; SF-6D, Short-Form Six-Dimension; SLR, systematic literature review; WPAI, Work Productivity and Activity Impairment Questionnaire.

J.1.2 Results

The electronic searches were performed on 2 September 2024 and updated on 2 July 2025. Across both the original and updated searches, following deduplication, 1732 articles were screened for inclusion. The number of articles excluded at the screening and full-text review stages were 1721 and 6, respectively. One relevant congress abstract was identified from supplementary searches. In total, six articles met the eligibility criteria and were included in this SLR (Figure 26).

Figure 26. PRISMA flow diagram – economic SLR



Abbreviations: HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

All six articles were congress materials: three abstracts and three posters (Sidhu et al. 2024) (Sidhu et al. 2024, Rich et al. 2024, Caravaca-Fontan et al. 2025a). The congress abstracts were presented at ERA 2024, (Lafayette et al. 2024b) ASN 2024 (Ndife et al. 2024) and the 2022 International Society of Nephrology (ISN) Frontiers Meeting (Vasudevan et al. 2022). The posters were presented at WCN 2024 (Sidhu et al. 2024),

ISPOR Europe 2024 (Rich et al. 2024) and ERA 2025 (Caravaca-Fontan et al. 2025a). None of the six articles were interventional.

Three articles utilised data from Adelphi Disease-Specific Programmes (DSPs), which are real-world evidence generation programmes. The Adelphi C3G and IC-MPGN DSPs involved a cross-sectional survey of nephrologists reporting on 1-9 consecutively consulted patients with C3G (Lafayette et al. 2024b, Sidhu et al. 2024) or a minimum of three consecutively consulted patients with primary IC-MPGN (Rich et al. 2024). Patients with C3G and IC-MPGN (or their parent/caregiver) were then invited to complete surveys to determine the self-reported impact and burden of the disease (Lafayette et al. 2024b, Sidhu et al. 2024). Two articles (one congress abstract and one poster) obtained data from the Adelphi C3G DSP (Sidhu et al. 2024, Lafayette et al. 2024b, Rich et al. 2024) conducted across eight countries (China, France, Germany, Italy, Japan, Spain, UK and the USA), while the third article (congress poster) used data from the Adelphi IC-MPGN DSP (Rich et al. 2024) conducted across five countries (France, Germany, Italy, Spain, and the USA).

The remaining articles included an Indian retrospective cohort study utilising hospital case records (congress abstract) (Vasudevan et al. 2022), a Spanish market research study using online questionnaires (congress poster) and a US retrospective analysis of electronic medical records and linked medical claims from the HealthVerity database (congress abstract) (Ndife et al. 2024).

Four articles evaluated patients with C3G: two studies focused on adults (Lafayette et al. 2024b, Sidhu et al. 2024), one included patients aged ≥12 years (Ndife et al. 2024) and one focused on children (Vasudevan et al. 2022). One study included both adults and children with primary IC-MPGN (Rich et al. 2024), and another included adults with C3G and IC-MPGN (not specified if primary) (Carcava Fontan et al.). Males accounted for 37-74% of the study populations across five articles (Sidhu et al. 2024, Lafayette et al. 2024b, Rich et al., Vasudevan et al. 2022, Ndife et al. 2024); one article did not report the sex of the patients (Caravaca-Fontan et al. 2025a).

The three multinational Adelphi DSP cross-sectional surveys captured data over a period of 1 year (Sidhu et al. 2024, Lafayette et al. 2024b, Rich et al.). The Indian retrospective chart review study collected data over a 7-year period (2013-2020) (Vasudevan et al. 2022), and the US retrospective analysis covered 5 years (2017-2022) (Ndife et al. 2024). The Spanish market research study collected data over the past 1 year (Caravaca-Fontan et al. 2025a).

For further details, please refer to the Excel data-extraction table spreadsheet.

A complete list of all included references is provided in Table 118, a list of excluded full-text references in Table 119.

Table 118. Complete list of included references in the economic SLR

Title	Author	Year
Socioeconomic and psycho-emotional impact of C3 glomerulopathy and immune complex membranoproliferative glomerulonephritis in adult patients in Spain	Fernando Caravaca-Fontan, Álvaro Madrid Aris, Marta Moreno, Marian Vidal Jorge, Julieta Nafissi, Manuel Praga Terente	2025
Self-reported quality of life in complement 3 glomerulopathy patients delineated by CKD stage: a real-world, multi-country survey	Sidhu R, Proudfoot C, Pannagl K *et al.*	2024
Quality of life and fatigue burden in individuals living with complement 3 glomerulopathy – a real-world study	Lafayette R, Sidhu R, Proudfoot C *et al.*	2024
Real-world survey on healthcare resource utilisation and physician-reported burden in patients with primary Immune Complex Membranoproliferative Glomerulonephritis	Carly Rich, Dima Decker, Lucía Quintana-Gallardo, James Jackson, Sarah Clayton, Kristie Fitzmaurice, Mollie Lowe, Katie Gordon, Mingyi Huang	2024
Clinico-pathological profile and outcomes of children with C3G in resource limited setting	Vasudevan A, Reddy S, Ghante A, Vankalakunti M	2022
Health care resource utilization (HCRU) burden in C3 glomerulopathy (C3G) in the United States: a retrospective linked electronic medical records (EMR) and claims database analysis	Ndife BC, Khairnar R, Bose A et al.	2024

Abbreviations: EMR, electronic medical records; HCRU, Health care resource utilisation; SLR, systematic literature review

Table 119. Complete list of excluded full-text references in the economic SLR

Author	Title	Year	Reason
Grewal, A. S. and Bansal, B. and Subbiah, A. and Bhowmik, D. and Agarwal, S. K. and Bagchi, S.	Health-Related Quality of Life in Adults with Primary Glomerular Diseases in India	2023	Outcome (data not specific for C3G/IC-MPGN; combined data for different glomerular diseases)
Ghani, M. and Alisan, B. and Barmas-Alamdari, D. and Attieh, R. M. and Jhaveri, K. D.	The Difficulties of Treating Complement-3-Mediated Glomerulopathy	2024	Article type
Java, A. and Fuller, L.	Establishing the Future Direction of Clinical Outcomes in C3 Glomerulopathy: Perspectives From a Patient and a Physician	2025	Article type
Lafayette, R. and Sidhu, R. and Proudfoot, C. and Pannagl, K. and Ndife, B. and Smeets, S. and Murphy, K. and Przybysz, R. and de Courcy, J. and Libby, S. and Sinha, S.	Wcn24-1688 Self-Reported Quality of Life in Complement 3 Glomerulopathy Patients Delineated by Ckd Stage: A Real-World, Multi-Country Survey	2024	Duplicate (identified and included from original searches)
Lafayette, R. and Sidhu, R. and Proudfoot, C. and Pannagl, K. and Ndife, B. and Smeets, S. and Murphy, K. and Przybysz, R. and Decourcy, J. and Libby, S. and Sinha, S.	Quality of life and fatigue burden in individuals living with Complement 3 Glomerulopathy - a real-world study	2024	Duplicate (identified and included from original searches)
Widiasta, A. and Labiba, A. N. and Tarigan, R.	Differences in Quality of Life Among Children with End-Stage Kidney Disease Undergoing Hemodialysis and Peritoneal Dialysis	2025	Population

J.2 Focused Search

No targeted literature search was performed to inform supplementary input to the health economic model.

Appendix K. Justification for Confidential Information

Table 120. Justifications regarding confidential information

Parameter	Justification
Patient numbers, epidemiology assumptions and uptake projections	Reflects internal estimates based on clinical expert input and company forecasts; not publicly available and business sensitive.
Cost-effectiveness results (ICER, QALYs, life years,	Derived from confidential company-owned economic modelling and not published elsewhere. Can be copied by competitors if made public.
Budget impact analysis	Contains confidential projections of financial impact based on internal assumptions and pricing information. Business sensitive.
Clinical data on file	Disclosure would reveal proprietary scientific information regarding treatment effects, patient outcomes, and internal analytical methods that are of significant commercial value to Sobi. Competitors could use this information to gain insights into Sobi's development and evidence-generation strategy without having made a comparable investment. Public disclosure could therefore harm Sobi's legitimate commercial interests and competitive position.
Value of saved kidneys, associated calculations and descriptions	Company-specific health system modelling that is not published and part of proprietary modelling approach.

Appendix L. Estimation of CKD and uPCR Disease Management Costs

To estimate costs in the CKD and uPCR states in the model, the health state costs used in NICE (2024) were used.

For each uPCR interval used in NICE (2024), a value was assigned, i.e.:

- [redacted] for uPCR [redacted] g/g
- [redacted] for uPCR [redacted] - [redacted] g/g
- [redacted] for uPCR [redacted] - [redacted] g/g
- [redacted] for uPCR [redacted] g/g

Corresponding cost points were then plotted for each CKD stage, e.g.:

Trendlines were then fitted to data (exponential was the best fit based on R-squared after testing the following functions: linear, logarithmic, power and exponential) for each CKD stage. Resulting equations were:

- [redacted]
- [redacted]
- [redacted]

Values for specific uPCR stages were calculated using values:

- [redacted] for uPCR [redacted]
- [redacted] for uPCR [redacted]
- [redacted] for uPCR [redacted]

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