

Single Technology Appraisal

Iptacopan for treating complement 3 glomerulopathy [ID6283]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Iptacopan for treating complement 3 glomerulopathy [ID6283]

Contents:

The following documents are made available to stakeholders:

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

- 1. Company submission from Novartis:**
 - a. Full submission
 - b. Addendum to company evidence submission
 - c. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. Kidney Research UK
 - b. MPGN/DDD Support Group
 - c. UK Kidney Association
 - d. UK Renal Pharmacy Group
 - e. NHS England
- 4. Expert personal perspectives from:**
 - a. Professor David Kavanagh – clinical expert, nominated by Novartis
 - b. Professor Matthew Pickering – clinical expert, nominated by MPGN/DDD Support Group
 - c. Lewis Brimble – patient expert, nominated by MPGN/DDD Support Group
- 5. External Assessment Report** prepared by Kleijnen Systematic Reviews
 - a. EAG report
 - b. EAG addendum
- 6. External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Iptacopan for treating complement 3 glomerulopathy (ID6283)

Company evidence submission

March 2025

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Abbreviations

Abbreviation	Definition
ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin to creatinine ratio
AE	Adverse event
aHUS	Atypical haemolytic uraemic syndrome
ANCOVA	Analysis of covariance
APD	Automated peritoneal dialysis
ARB	Angiotensin receptor blocker
Bb	Cleaved Factor B
b.i.d.	Twice daily
BNF	British National Formulary
C3	Complement component 3
C5	Complement component 5
C3G	Complement 3 glomerulopathy
C3GN	C3 glomerulonephritis
CAPD	Continuous ambulatory peritoneal dialysis
CFHR5	Complement Factor H-related protein 5
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CfB	Change from baseline
CKD	Chronic kidney disease
CKD-EPI	The Chronic Kidney Disease Epidemiology Collaboration
CS	Corticosteroid
CSR	Clinical study report
CV	Cardiovascular
DDD	Dense deposit disease
DSA	Deterministic sensitivity analysis
DSP	Disease Specific Programme
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Electronic marketing information tool
ESRD	End-stage renal disease
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FMV	First morning void
GFR	Glomerular filtration rate
HTA	Health technology assessment
HCRU	Healthcare resource use
HD	Haemodialysis
HR	Hazard ratio

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Abbreviation	Definition
HRQoL	Health-related quality of life
HST	Highly Specialised Technologies
I/C	Intercurrent events
ICER	Incremental cost-effectiveness ratio
IC-MPGN	Immune complex-mediated membranoproliferative glomerulonephritis
IgAN	Immunoglobulin A nephropathy
INHB	Incremental net health benefit
IPD	Individual patient data
ITC	Indirect treatment comparison
IQR	Interquartile range
J2R	Jump to reference
KDIGO	Kidney Disease Improving Global Outcomes
KRT	Kidney replacement therapy
LYG	Life years gained
MA	Marketing authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MMF	Mycophenolate mofetil
MMRM	Mixed Model for Repeated Measures
MPA	Mycophenolic acid
MPGN	Membranoproliferative glomerulonephritis
MPS	Mycophenolate sodium
MRA	Mineralocorticoid receptor antagonist
MTA	Multiple technology appraisal
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OR	Odds ratio
PAS	Patient access scheme
PD	Peritoneal dialysis
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal haemoglobinuria
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PY	Patient-years
QoL	Quality of life
QALY	Quality-adjusted life year
RaDaR	National Registry of Rare Kidney Diseases
RAS	Renin-angiotensin system
RCT	Randomised controlled trial
SAE	Serious adverse event

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Abbreviation	Definition
SAF	Safety set
SCR	Screening set
SD	Standard deviation
SGLT2i	Sodium-glucose co-transporter-2 inhibitor
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
STA	Single Technology Appraisal
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TLR	Targeted literature review
UACR	Urine albumin to creatinine ratio
UK	United Kingdom
US	United States
UPCR	Urine protein to creatinine ratio
VAT	Value added tax
WTP	Willingness-to-pay

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

Complement 3 glomerulopathy (C3G) is an ultra-rare chronic and progressive kidney disease which is characterised by deposits of complement component 3 (C3) in the glomeruli. C3G is commonly diagnosed at a young age¹⁻³

- C3G is caused by overactivation of the complement alternative pathway of the immune system,^{1, 4, 5} which leads to the deposition of C3 and its cleavage products within the glomeruli of the kidneys, triggering inflammation and glomerular injury.^{5, 6} As glomeruli are injured, normal kidney function becomes impaired, with wide-ranging consequences including proteinuria (protein in the urine), haematuria (blood in the urine), renal dysfunction, hypertension (high blood pressure) and fatigue⁷⁻¹⁰
- C3G is a progressive disease, in which individuals experience continuous symptom worsening alongside irreversible kidney damage, before reaching kidney failure.⁵ Patients reaching kidney failure require chronic dialysis or kidney transplantation¹¹⁻¹³
- Based on registry data, the current prevalence of C3G in the United Kingdom (UK) is estimated as 0.37 in 50,000, with an estimated 427 people living in England with C3G in 2024.^{3, 14, 15} C3G is commonly diagnosed in young people, with the median age at diagnosis reported as 21–23 years old^{1, 16, 17}

With current treatments, approximately 50% of patients with C3G progress to kidney failure within 10 years of diagnosis,^{3, 16, 18, 19} and the rate of C3G recurrence following kidney transplantation is high (55–85%)^{5, 19-24}

- There are currently no targeted therapies for C3G, and currently used treatments predominantly constitute supportive care with limited evidence in C3G²⁵
- Angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) are recommended as initial therapy to reduce proteinuria and manage hypertension.²⁵ Further treatment options include mycophenolate mofetil (MMF) and/or corticosteroids (CS), or sodium-glucose co-transporter-2 inhibitors (SGLT2is), although clinical trial enrolment is often preferred by UK clinicians.²⁵⁻²⁷ The use of eculizumab in the UK is very limited and restricted to highly aggressive cases of post-transplant recurrent C3G²⁶⁻²⁸
- None of the currently available treatments address the underlying pathophysiology of C3G. Many C3G patients therefore progress to kidney failure and become reliant on chronic dialysis or require a kidney transplant at a young age, with the disease commonly recurring following transplantation^{5, 19-24}
- Disease progression is associated with increasing clinical, humanistic and economic burden, including co-morbidities, reduced quality of life (QoL), costs for the National Health Service (NHS), and productivity losses for people with C3G and their carers. There is therefore an unmet need in C3G for targeted therapies which slow disease progression

Iptacopan, a novel, oral proximal complement inhibitor, is expected to be the first targeted treatment for C3G²⁹

- Iptacopan is a twice daily (b.i.d.) oral complement inhibitor targeting Factor B,²⁹ and expected to be the first targeted treatment addressing the underlying pathophysiology of C3G and therefore the high unmet need of this ultra-rare, progressive condition

- It is anticipated that iptacopan will be licensed for the treatment of adult patients with C3G in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated³⁰

1.1 Decision problem

This submission covers the full expected marketing authorisation of iptacopan for this indication. The decision problem addressed in this submission is provided in Table 1, which outlines any differences from the National Institute for Health and Care Excellence (NICE) final scope.³¹

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with C3G	Adults with C3G	In line with final scope. The decision problem reflects the currently available evidence and expected licensed population. A clinical trial for iptacopan in adolescents with C3G (12 to below 18 years of age) is currently ongoing,³² and a licence extension to adolescents will be pursued at a later date subject to the trial read-out
Intervention	Iptacopan	Iptacopan	In line with final scope. This submission considers iptacopan 200 mg b.i.d. in combination with established clinical management, comprising of ACEis/ARBs (unless not tolerated or contraindicated), with some patients also being on CS, MMF and/or SGLT2is. This aligns with the design of the iptacopan clinical trials, in which patients were administered iptacopan on top of these background therapies³³⁻³⁵
Comparator(s)	Established clinical management without iptacopan, which may include: • ACEis • ARBs • CS • MMF • SGLT2is In people who have previously had a kidney transplant and who have highly aggressive C3G recurrence as specified in the NHS	Established clinical management without iptacopan, which may include: • ACEis • ARBs • CS • MMF • SGLT2is	Established clinical management is considered as comparator in line with the final scope. A comparison with eculizumab was not undertaken due to limitations of the evidence base (see Section 2.9). However, eculizumab is considered of limited relevance as a comparator for this submission, for the following reasons: • Use in UK clinical practice is uncommon.^{26, 36} With the NHS England commissioning policy restricting use to a small subgroup among patients with post-

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	England clinical commissioning policy for eculizumab: Eculizumab		transplant recurrence,²⁸ on average only 1 person per year was able to access eculizumab as a treatment for C3G since the commissioning policy was put in place in 2017.^{27, 36} The use of eculizumab is limited to patients with highly aggressive recurrent disease. Amongst others, the criteria require evidence of a significant decline of transplant function (>20% decline in estimated glomerular filtration rate [eGFR]) within the previous three months.²⁸ Treatment with iptacopan, on the other hand, can be started as soon as recurrence is diagnosed via biopsy of the transplanted kidney, before the onset of clinical signs such as eGFR decline; this is in line with the available clinical trial evidence (see Section 2) and the draft summary of product characteristics (SmPC; section 4.2).^{30, 37} As such, UK clinicians have advised that they would want to start iptacopan at an earlier point of disease recurrence than eculizumab,²⁷ which further reduces the relevance of eculizumab as a comparator for the intended positioning of iptacopan
Outcomes	The outcome measures to be considered include: - Kidney function (for example, eGFR) - Proteinuria - Disease progression (need for kidney transplant and/or dialysis) - Mortality	The outcome measures presented in this submission include: - Kidney function (eGFR) - Proteinuria (change from baseline in urine protein-to-creatinine ratio [UPCR]) - Disease progression (dialysis)	Data for these outcomes are presented in this submission to the extent to which they are available. Data for progression to dialysis/transplant as well as mortality data are limited due to the follow-up duration of the iptacopan clinical trials^{33, 38}

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	- Adverse effects of treatment - Health-related quality of life	and/or transplant) - Mortality - Adverse effects of treatment - Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of iptacopan is conditional on the results of renal biopsy. The economic modelling should include the costs associated with diagnostic testing in people who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 4.8 of the guidance development manual³⁹	The economic modelling approach presented in this submission is in line with the reference case	The cost of kidney biopsy was not modelled in this submission as patients are biopsied to obtain a diagnosis of C3G, irrespective of the existence of iptacopan, and no additional biopsy is required to establish eligibility for iptacopan, as confirmed by UK clinical expert opinion.⁴⁰ Therefore, based on expert advice, costs associated with diagnostic testing have not been included⁴⁰
Subgroups to be considered	If evidence allows, the following subgroups will be considered: People who have and have not had a kidney transplant	Clinical evidence is presented for the efficacy and safety of iptacopan in patients who have not had a kidney transplant (native kidney patients) and	The randomised, placebo-controlled iptacopan Phase 3 trial APPEAR-C3G included patients with native kidney disease. While the Phase 2 trial included a cohort of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• People with C3 glomerulonephritis (C3GN) • People with dense deposit disease (DDD) • People with complement Factor H-related protein 5 (CFHR5) nephropathy	in patients who had disease recurrence following a kidney transplantation (post-transplant recurrent patients). Economic modelling is based on data in native kidney patients.	patients with post-transplant recurrence of C3G, the trial was single-arm and the sample size was considered too small (N=11) to robustly inform economic modelling in a post-transplant subgroup. Therefore, the economic analyses presented are based on data in native kidney patients. Given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients.^{27, 40} Furthermore, the approach to model only a native kidney population aligns with that taken in previous NICE appraisals in other chronic kidney diseases, with the NICE recommendations for these treatments not excluding transplanted patients even where transplanted patients were excluded from the clinical trials. Further details are provided in Section 2.7. This submission does not present subgroup analyses for people with C3GN and DDD apart from a subgroup analysis of the primary endpoint of APPEAR-C3G, where interpretability of results is limited by the small sample size and imbalance between groups (DDD patients in iptacopan arm n=9, placebo arm n=1). Whilst a distinction between C3GN and DDD is made based on kidney tissue biopsy findings,^{41, 42} the clinical presentation, disease course, and management of these C3G subtypes are generally considered to be

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			consistent. ^{5, 18, 19, 43} Consequently, the clinical and cost-effectiveness of iptacopan are not expected to differ between people with C3GN and DDD. ⁴⁰ Similarly, CFHR5 nephropathy is a subtype of C3GN, caused by a genetic mutation endemic to people of Cypriot origin, ^{44, 45} and clinical and cost-effectiveness of iptacopan are not expected to differ from other people with C3G ⁴⁰
Special considerations including issues related to equity or equality	Equality impact assessment – Scoping:⁴⁶ <i>Potential equality issues identified during the scoping process</i> - Children (under 12 years of age) are excluded from the licence. Furthermore, the company indicated that its submission will exclude young people (under 18 years of age). Consultees noted that access for people of all ages should be considered - There is a longer waiting time for kidney transplants for black people and people with an Asian family background compared to white people. A third of people (35 per cent) waiting for a kidney across the UK are from minority ethnic groups but in 2017/18, of those providing their ethnicity when registering on the NHS Organ Donor Register, only 3.3 per cent had an Asian family background, 1 per cent were black and 2 per cent were mixed race	Novartis supports access to treatment for all people with C3G regardless of their age and ethnicity. While the currently available iptacopan clinical trial results and expected licensed indication are limited to adults, Novartis is committed to pursuing a licence extension and access to iptacopan for younger people with C3G as soon as the available evidence permits. The iptacopan clinical trials in C3G enrolled patients globally, including in the UK. In the APPEAR-C3G study, 24.3% of participants were of Asian ethnicity and 2.7% were of Black or African American ethnicity³³	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	<i>Preliminary view as to what extent these potential equality issues need addressing by the Committee</i> The Committee should consider iptacopan within its marketing authorisation (adult population), however the Committee may consider whether Commissioning Medicines for Children in Specialised Services applies in this instance.⁴⁷ The Committee should consider whether the longer waiting times faced by black people and people of Asian family backgrounds represents a health inequality, and if so the impact of guidance on this inequality		

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; b.i.d., twice daily; C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; CFHR5, complement Factor H-related protein 5; CS, corticosteroids; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; mg, milligram; MMF, mycophenolate mofetil; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UK, United Kingdom; UPCR, urine protein-to-creatinine ratio.

Source: Iptacopan for treating complement 3 glomerulopathy. Final Scope (ID6283);³¹ Iptacopan for treating complement 3 glomerulopathy. Equality Impact Assessment (ID6283).⁴⁶

1.2 Description of the technology being evaluated

Table 2 summarises the technology (iptacopan) being evaluated in this submission.

Table 2: Technology being evaluated

UK approved name and brand name	Approved name: Iptacopan Brand name: FABHALTA®
Mechanism of action	Iptacopan is a proximal complement inhibitor that targets Factor B to selectively inhibit the complement alternative pathway. ²⁹ In C3G, overactivation of the complement alternative pathway leads to deposition of C3 within the glomeruli, triggering inflammation and glomerular injury. ⁴⁸ Iptacopan selectively blocks alternative pathway overactivation by inhibiting alternative pathway-related C3 convertase activity, leading to decreased cleavage of C3 and reduced C3 deposition in the kidney ³⁷
Marketing authorisation/CE mark status	In August 2024, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a marketing authorisation (MA) for iptacopan as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. ⁴⁹ Following submission of an application for an indication extension to the European Medicines Agency (EMA), the Committee for Medicinal Products for Human Use (CHMP) granted a positive opinion for the C3G indication in February 2025. ⁵⁰ An application for a licence extension to C3G has been submitted to the MHRA in [REDACTED] MHRA MA for C3G is expected in [REDACTED]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication of iptacopan in C3G is as follows: "Iptacopan is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated" ³⁰ Based on the currently applicable SmPC for the PNH indication and draft SmPC for the C3G licence extension, ^{30, 49} iptacopan is expected to be contraindicated in the following cases: • Hypersensitivity to the active substance or to any of the excipients • In patients who are not currently vaccinated against <i>Neisseria meningitidis</i> (<i>N. meningitidis</i>) and <i>Streptococcus pneumoniae</i> (<i>S. pneumoniae</i>), unless the risk of delaying iptacopan treatment outweighs the risk of developing an infection from these encapsulated bacteria • For initiation in patients with unresolved infection caused by encapsulated bacteria, including <i>N. meningitidis</i>, <i>S. pneumoniae</i> or <i>Haemophilus influenzae</i> (<i>H. influenzae</i>) type B
Method of administration and dosage	Iptacopan 200 mg capsules are administered twice daily (b.i.d) as an oral treatment ³⁰
Additional tests or investigations	No additional tests or investigations are required to identify people with C3G eligible for treatment with iptacopan. The use of complement inhibitors may predispose patients to serious infections with encapsulated bacteria. Patients treated with iptacopan must be vaccinated against <i>N. meningitidis</i> and <i>S. pneumoniae</i> , while vaccination against <i>H. influenzae</i> type B is recommended. Patients should be vaccinated ≥2 weeks before starting treatment or receive

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	antibacterial prophylaxis until 2 weeks after vaccination. Patients may be revaccinated in accordance with local guidelines ³⁰
List price and average cost of a course of treatment	The list price of iptacopan 200 mg is £26,500.00 per 56 capsules, excluding VAT ⁵¹
Patient access scheme (if applicable)	A confidential patient access scheme (PAS) is in place, with a PAS price for iptacopan 200 mg of £[REDACTED] per 56 capsules ([REDACTED]% discount). [REDACTED]

Abbreviations: b.i.d., twice daily; C3, complement 3 protein; C3G, complement 3 glomerulopathy; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, Patient Access Scheme; PNH, paroxysmal nocturnal haemoglobinuria; RAS, renin angiotensin system; SmPC, summary of product characteristics; VAT, value added tax.

Sources: Schubart et al. 2019;²⁹ Bomback et al. 2022;⁴⁸ Wong et al. 2023;³⁷ MHRA. 2024 (FABHALTA [iptacopan] SmPC);⁴⁹ Novartis Data on File. 2024 (FABHALTA [iptacopan] draft SmPC);³⁰ BNF. 2024 (Iptacopan. Medicinal Forms);⁵¹ NICE. 2024 (Iptacopan for treating paroxysmal nocturnal haemoglobinuria [TA1000]).⁵²

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

1.3.1 Disease pathophysiology

Complement 3 glomerulopathy (C3G) is an ultra-rare, complex and progressive chronic kidney disease, which is characterised by deposits of complement component 3 (C3) in the glomeruli.^{1, 2}

The complement system, a crucial part of the innate immune system, consists of more than 50 small proteins.⁵ When stimulated, these proteins form a cascade that promotes inflammation and the activity of the innate immune system.^{1, 4, 5, 48, 53, 54} The complement system can be activated by three pathways: the classical, lectin and alternative pathways (Figure 1).⁵

The classical and lectin pathways remain inactive unless triggered; the alternative pathway, however, remains constitutively active at a low level and plays a pivotal role in providing a rapid defence mechanism against a wide range of pathogens and amplifying the complement response.^{4, 5, 55, 56}

The diagram illustrates the activation of the complement system, categorized into three pathways: Classical, Lectin, and Alternative. The process is divided into three stages: Proximal, Amplification, and Terminal.

- Classical Pathway:** Immune complexes trigger the activation of C3 convertases (C4b2b).
- Lectin Pathway:** Carbohydrate motifs on the surface trigger the activation of C3 convertases (C3(H₂O)Bb).
- Alternative Pathway:** Constitutively active at low level.

Proximal Stage: C3 convertases (C4b2b) cleave C3 into C3a and C3b. C3b is then cleaved into C3a and C3b. C3b is then cleaved into C3a and C3b. C3b is then cleaved into C3a and C3b.

Amplification Stage: C3b is cleaved into C3a and C3b. C3b is then cleaved into C3a and C3b. C3b is then cleaved into C3a and C3b.

Terminal Stage: C5 convertases (C4b2bC3b) cleave C5 into C5a and C5b. C5b is then cleaved into C5a and C5b. C5b is then cleaved into C5a and C5b.

Effects:

- C3b:** Accumulation of C3 fragments.
- Inflammation:** Mediated by anaphylatoxins C3a and C5a.
- Kidney damage:** Mediated by C5b9 (MAC).

Sources: Adapted from Bomback et al. 2022,⁴⁸ and Keir et al. 2012.⁵⁵

As glomeruli are injured, normal kidney function becomes impaired, with wide-ranging consequences. These can include haematuria (blood in the urine), proteinuria (protein in the urine), oliguria (low urine output), and kidney damage.^{5, 57} The kidney damage observed as a result of continued complement activity is progressive and mostly irreversible.⁵

While incidence and prevalence are difficult to ascertain, given the rare nature of C3G and its relatively recent definition as a distinct disease in 2013,⁴² C3G is considered an ultra-rare disease.

No studies reporting population-based prevalence estimates for C3G could be identified. The National Organization for Rare Disorders (NORD) website states an estimated prevalence of

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C3G of 2–3 per 1,000,000 people, i.e. 0.1–0.15 per 50,000 people.⁵⁸ Based on data from the National Registry of Rare Kidney Diseases (RaDaR), which includes data from 109 renal centres across the UK,⁵⁹ Novartis estimates that there are currently approximately 505 prevalent patients with C3G in the UK overall, or 427 patients in England,^a equating to a prevalence of 0.37 in 50,000.^{3, 14, 59, 60}

C3G predominantly affects young people aged under 40 years. The median age at diagnosis is reported as 21–23 years old, with C3G commonly diagnosed under 18 years of age.^{1, 16, 18, 19} In a recent analysis of data from 258 UK patients with C3G in RaDaR,⁵⁹ the median age at diagnosis was 22 years (interquartile range [IQR]: 12–45 years), with 44% of patients diagnosed below the age of 18 years.¹⁷

1.3.3 Presentation and diagnosis

Patients with C3G often present with a range of signs and symptoms, including proteinuria, haematuria and varying degrees of renal dysfunction.^{5, 57} Other signs and symptoms may include hypertension (high blood pressure), fatigue, oedema (swelling of some areas of the body, including feet, hands and ankles), and oliguria (low urine output).⁷⁻¹⁰ Some patients with C3G present with nephrotic syndrome, which is a term used to describe the association of high levels of proteinuria (urine protein-creatinine ratio [UPCR] >300–350 mg/mmol) with peripheral oedema, hypoalbuminemia (serum albumin <25 g/L) and severe hyperlipidaemia (total cholesterol often >10 mmol/L).⁶¹

While clinical presentation plays a role in diagnosis, laboratory tests and a kidney biopsy are required for differentiation between various glomerular diseases including other forms of membranoproliferative glomerulonephritis (MPGN) or immunoglobulin A nephropathy (IgAN).^{5, 25, 42}

Genetic and antibody testing is used to determine whether there is an underlying complement abnormality.⁴² For example, low levels of serum C3 combined with normal levels of another complement component, C4, indicate activation of the alternative complement pathway.⁴² Urine analysis often shows the presence of red blood cells, white blood cells, and protein.⁶²

Kidney biopsy is required for a definitive diagnosis of C3G.¹ C3G is divided into two subtypes, dense deposit disease (DDD) and complement 3 glomerulonephritis (C3GN), according to kidney biopsy findings at the electron microscopy level.⁴² The clinical presentation and prognosis are consistent between subtypes and clinical management remains the same.^{5, 18, 19, 43}

1.3.4 Disease course

C3G is a progressive disease, in which individuals experience continuous symptom worsening alongside irreversible kidney damage, before reaching kidney failure.⁵ C3G carries one of the

^a As of November 2024, RaDaR contained data from overall 1,232 patients with membranoproliferative glomerulonephritis (MPGN).⁶⁰ The MPGN cohort in RaDaR comprises patients with C3G as well as patients with immune complex-mediated MPGN (IC-MPGN), although exact diagnosis is not always captured in RaDaR data. In an analysis conducted in 2023, among 287 patients with exact diagnosis recorded, 47% had C3G and 53% had IC-MPGN.³ Applying this split to the entire cohort (N=1,232) and considering that 157 patients of the overall MPGN cohort in RaDaR had died prior to July 2022,¹⁴ the number of prevalent C3G patients in RaDaR can be estimated as a maximum of 505 patients for the UK overall, or 427 patients for England.¹⁵

highest risks for irreversible kidney failure of all primary glomerular diseases, with approximately 50% of patients progressing to kidney failure within 10 years of diagnosis.^{3, 16, 18, 19}

1.3.4.1 Glomerular filtration rate

Kidney function in individuals with C3G is impacted due to damage caused to the glomeruli, impairing their ability to filter blood effectively, leading to a reduced glomerular filtration rate (GFR).⁶³ The filtration rate is usually monitored via an estimated GFR (eGFR), which is a measure of kidney filtration calculated based on serum creatinine levels, age, sex, and other factors (measured in mL/min/1.73 m² to adjust for body surface area).¹³ The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR creatinine equation is considered the preferred method of calculating eGFR in adults with glomerular diseases.²⁵

Tracking eGFR, as a marker of kidney damage, provides valuable insights into the progression of C3G, with eGFR levels used to define stages of disease progression (Section 1.3.4.3). An eGFR ≥ 90 mL/min/1.73 m² is considered to represent normal kidney function.²⁵ In a recent analysis of 109 UK patients with C3G and eGFR data available in RaDaR, the median eGFR at diagnosis was 71 mL/min/1.73 m².¹⁷ A progressive decline in eGFR in C3G patients is associated with poor outcomes.^{3, 64}

1.3.4.2 Proteinuria

Proteinuria is a key sign of C3G and can be assessed by the level of protein excretion into urine. This can be calculated as urine protein to creatinine ratio (UPCR) or urine albumin to creatinine ratio (UACR), with UPCR generally preferred for glomerular diseases including C3G.^{11, 25, 27, 65} Proteinuria may be measured using a first morning void (FMV) sample, when the first urine of the day is collected for a concentrated analysis, or all samples collected over a 24-hour period.⁶⁶

A UPCR of <50 mg/mmol is considered to be in the normal range for adults, with a higher UPCR associated with worse kidney outcomes.^{65, 67, 68} In an analysis of UK patients with C3G and UPCR data available in RaDaR (n=91), median UPCR at diagnosis was 442 mg/mmol (IQR: 140–871 mg/mmol).¹⁷ Overall, 82% of patients had UPCR ≥ 100 mg/mmol at diagnosis,¹⁷ indicating increased risk of progression to kidney failure;²⁵ 66% of patients had nephrotic-range proteinuria (UPCR ≥ 300 mg/mmol) at time of diagnosis.¹⁷ An international cross-sectional study further showed high levels of persistence of proteinuria with currently available treatments, with 62% of 263 patients with C3G having UPCR ≥ 1 g/day (≥ 113 mg/mmol) despite receiving treatment.¹⁰ Among 50 patients who had been receiving treatment for C3G for more than two years at the time of the analysis, 44% still had UPCR ≥ 1 g/day.¹⁰

Proteinuria is a key risk factor for progression to kidney failure, as evidenced widely for chronic kidney disease (CKD) more generally, and glomerular diseases including C3G and IgA nephropathy.^{3, 17, 25, 64, 67, 69-72} Recent analyses of registry data from patients with C3G in the UK (RaDaR) and Spain found that reduction in proteinuria was significantly associated with a lower risk of kidney failure.^{3, 72}

1.3.4.3 Clinical staging

CKD is classified into stages, which can be used to define the level of risk and monitor for disease progression in C3G over time. eGFR, as measure of kidney function, provides information on the level of damage in the glomeruli and can be used to categorise CKD into CKD stages 1 (eGFR ≥ 90 mL/min/1.73 m²; normal kidney function) to 5 (eGFR <15 mL/min/1.73 m²; kidney failure).^{11, 13, 73, 74} The international Kidney Disease Improving Global Outcomes (KDIGO)

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guideline recommends classifying CKD based on cause, GFR category (G1–G5), and albuminuria category (A1–A3; measured by albumin to creatinine ratio [ACR]; Table 3).^{11, 73, 74} For both eGFR and ACR, a higher category indicates more severe kidney disease with a higher risk of adverse outcomes.^{11, 73}

Table 3: CKD stages: Risk of adverse outcomes in adults by GFR and ACR category

		ACR category A1 Normal to mildly increased (<3 mg/mmol)	ACR category A2 Moderately increased ^a (3–30 mg/mmol)	ACR category A3 Severely increased (>30 mg/mmol)
CKD stage 1	GFR category G1^b Normal or high (≥90 mL/min/1.73 m ²)	Low risk. No CKD if there are no other markers of kidney damage	Moderate risk	High risk
CKD stage 2	GFR category G2^b Mildly decreased ^a (60–89 mL/min/1.73 m ²)	Low risk. No CKD if there are no other markers of kidney damage	Moderate risk	High risk
CKD stage 3a	GFR category G3a Mildly to moderately decreased (45–59 mL/min/1.73 m ²)	Moderate risk	High risk	Very high risk
CKD stage 3b	GFR category G3b Moderately to severely decreased (30–44 mL/min/1.73 m ²)	High risk	Very high risk	Very high risk
CKD stage 4	GFR category G4 Severely decreased (15–29 mL/min/1.73 m ²)	Very high risk	Very high risk	Very high risk
CKD stage 5	GFR category G5 Kidney failure (<15 mL/min/1.73 m ²)	Very high risk	Very high risk	Very high risk

^aRelative to the normal range for a young adult. ^bIn the absence of evidence of kidney damage, neither G1 nor G2 fulfils the criteria for CKD.

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; GFR, glomerular filtration rate.

Sources: Table adapted from Stevens et al. 2024 (KDIGO),⁷³ NICE. 2021 (NG203),¹¹ and NHS. 2023.¹³

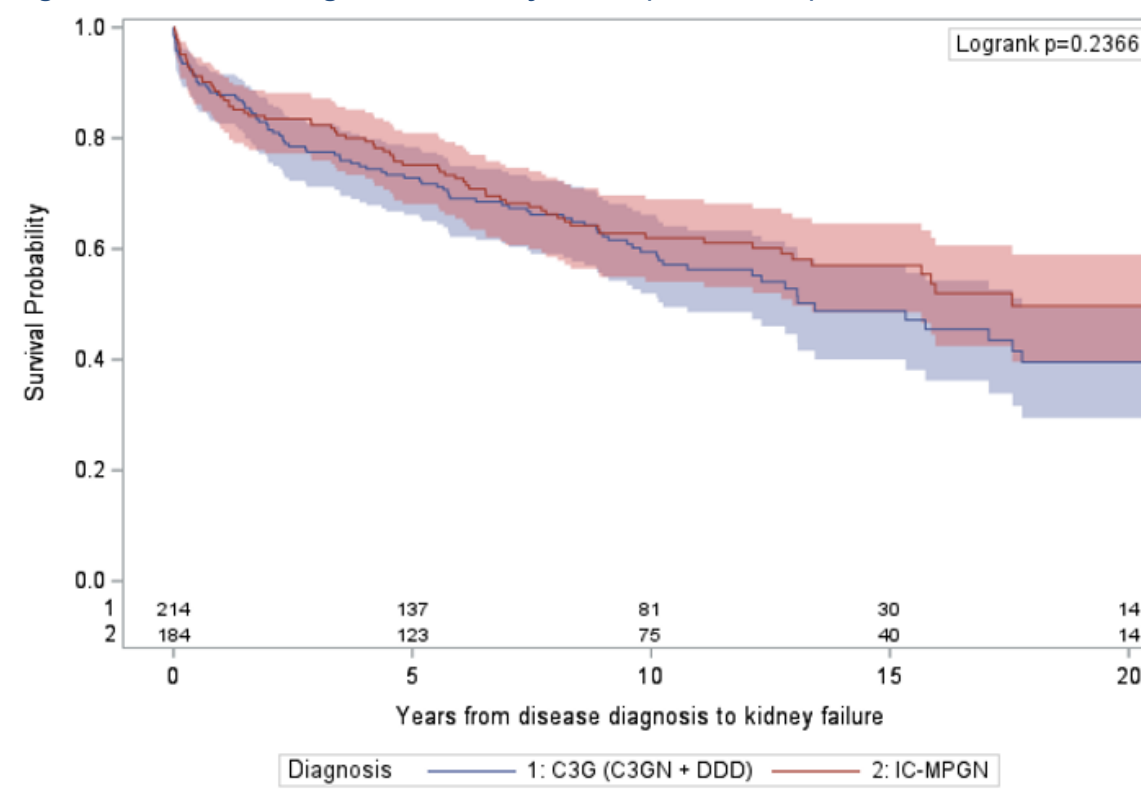
1.3.4.4 Kidney failure and kidney replacement therapy

Long-term management of C3G typically involves regular monitoring of kidney function, blood pressure control, and the use of specific medications to reduce proteinuria and inflammation (see Section 1.3.5). However, as these treatments do not target the underlying cause of the disease, patients still progress to kidney failure, with approximately 50% of patients with C3G progressing to kidney failure within 10 years of diagnosis.^{3, 16, 18, 19} In a study by Bomback et al. 2018, of 111 patients with C3G in the United States (US), 40% of patients progressed to advanced CKD, kidney failure or death, over a mean follow-up period from diagnosis of 6 years.¹⁸ In a retrospective analysis of C3G patients in the UK and Ireland by Medjeral-Thomas et al. 2014, 29% of 70 patients with adequate follow-up data progressed to kidney failure after a median follow-up of 28 months (IQR: 7–84 months).¹⁶ A case series by Servais et al. 2012 in a French multi-centre study identified that 36.5% of 134 patients with C3G progressed to kidney failure within 10 years of diagnosis.¹⁹ Similarly, a recent analysis of data from UK patients with C3G in

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RaDaR reported an estimated median time from diagnosis to kidney failure of 13.4 years (95% confidence interval [CI]: 10.3, 17.8 years) (Figure 2).¹⁷

Figure 2: Time from diagnosis to kidney failure (RaDaR data)



Median Survival time:

C3G – 13.4 years (95% CI 10.3, 17.8)

IC-MPGN – 17.6 years (95% CI 12.9, 25.9)

Footnote: Kidney failure defined as sustained eGFR <15 mL/min/1.73m², initiation of chronic dialysis or receipt of kidney transplant. 40 patients with C3G and 25 patients with IC-MPGN were excluded from the analysis due to reaching kidney failure prior to diagnosis.

Abbreviations: C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; CI, confidence interval; DDD, dense deposit disease; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; RaDaR, National Registry of Rare Kidney Diseases.

Source: RaDaR analysis, 2024.¹⁷

Given the young average age at diagnosis (median age 21–23 years),^{1, 16, 17} and short median time to kidney failure, patients with C3G are often reliant on chronic dialysis or require a kidney transplant at a young age. In the prevalent RaDaR cohort of 240 people with C3G and a mean age of 40.6 years (standard deviation [SD]: 19.34), 51% had reached kidney failure at the time of analysis.¹⁷

Patients reaching kidney failure require kidney replacement therapy (KRT) in the form of dialysis or kidney transplantation.^{11, 12} Dialysis is a mechanical procedure to remove waste products and excess fluid from the blood, and can take two forms, haemodialysis (HD) and peritoneal dialysis (PD).⁷⁵⁻⁷⁸ HD involves the individual's blood being transferred in and out of a dialysis machine and is typically performed at dialysis centres, though this can also be performed at home.^{77, 79} HD sessions typically occur three times a week, taking approximately four hours per session.⁷⁷ PD involves the infusion of dialysis solution into the peritoneal cavity (the space within the abdomen that contains the intestines, the stomach, and the liver) through a catheter, which allows the

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lining of the abdomen to act as a filter to remove waste products and excess fluid from the blood.^{77, 78} PD can take the form of continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), and is administered at home.⁷⁷ CAPD is repeated approximately four times a day, with each session lasting 30–40 minutes. APD is performed daily for 8–10 hours, usually overnight.⁷⁷

Once individuals with C3G have progressed to kidney failure, they may receive a kidney transplant if a suitable living or deceased donor kidney is available. Transplants can also be pre-emptive, providing patients with a transplant prior to the start of dialysis.⁸⁰ For patients to be eligible for a transplant, they must be in good general health as there is a risk of significant physical side effects, most notably post-transplant infection or acute rejection.^{81, 82} Immunosuppressants are prescribed long-term following kidney transplantation to prevent organ rejection, and are also associated with a number of side effects.^{13, 82}

1.3.4.5 Post-transplant recurrence and graft failure

As C3G is characterised by overactivation of the complement alternative pathway, which occurs upstream of the kidneys,⁵ kidney transplantation does not address the underlying pathophysiology of C3G.²³ Therefore, C3G commonly recurs following kidney transplantation, with recurrence rates reported to be between 55–85%, with a median time to recurrence of 14–28 months.^{5, 19, 20, 22-24, 83}

As a consequence of disease recurrence, the risk of graft failure in C3G is high, with reported graft failure rates of 50% among patients with disease recurrence, and a median time from transplant to graft failure of 77 months.²⁴ Following graft failure, patients are required to either return to dialysis or receive another kidney transplant. RaDaR data from patients with C3G indicate a median time to graft failure post-transplant of 6.5 years; among 75 prevalent kidney transplant recipients with C3G, 14 patients (18.7%) had received two or more kidney transplants at the time of analysis.¹⁷

1.3.4.6 Mortality

While data for C3G as an ultra-rare disease are limited, decline in kidney function is widely acknowledged to be associated with an increased risk of complications of kidney disease, including cardiovascular disease and mortality.^{47, 70, 84-86} An analysis in 27,285 people from the UK with rare kidney diseases included in RaDaR (including 1,089 people with either C3G or MPGN) estimated a standardised mortality ratio (SMR) of 2.29 (95% CI: 2.09, 2.49) compared to the general population in England and Wales; for people with rare kidney diseases with kidney failure (eGFR ≤ 15 mL/min/1.73 m² or receiving KRT) the SMR was 3.99 (95% CI: 3.55, 4.42).¹⁴

The mortality burden of CKD on an individual level is largest in younger patients, with a recent US study estimating that a 20-year-old with CKD loses on average 15.6 life years compared with a 20-year-old without CKD, while a 70-year-old with CKD would on average lose 3.9 life years compared to a similarly aged individual without CKD.⁸⁷ While these values are not C3G-specific and mortality in rare kidney diseases may be lower than in CKD overall,¹⁴ these data are pertinent given that individuals with C3G tend to be diagnosed at a young age (median age at diagnosis 21–23 years old) and approximately 50% will progress to kidney failure within 10 years of diagnosis.^{1, 19, 88, 89}

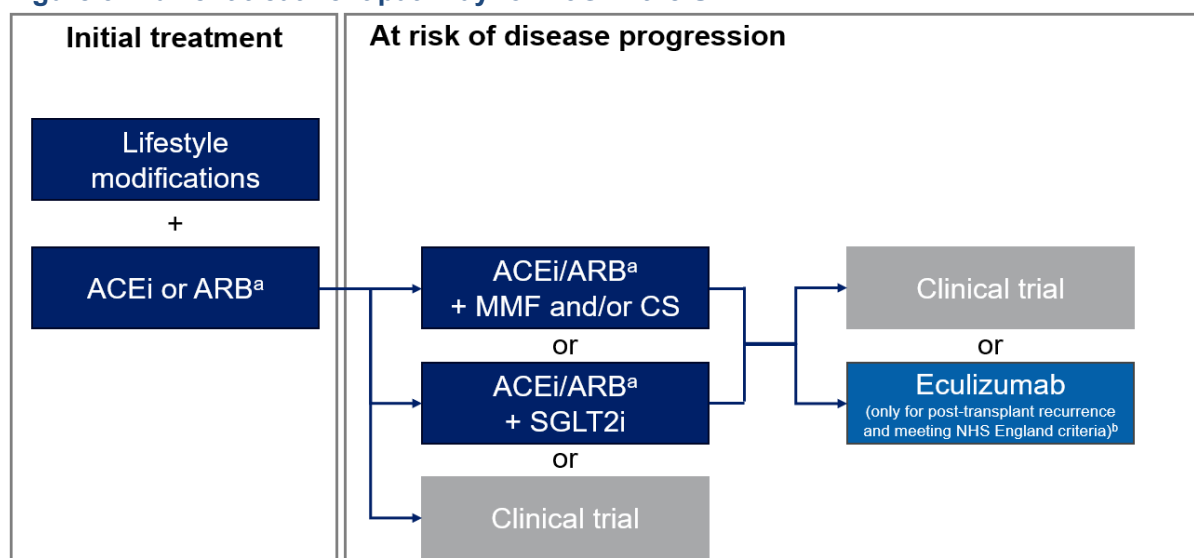
1.3.5 Treatment pathway

Ultimately, maintaining kidney function and preventing kidney failure are the key treatment goals in C3G.²⁶ However, currently available therapies do not address the underlying pathophysiology of C3G, and predominantly constitute supportive care.^{25, 26}

KDIGO published international clinical practice guidelines in 2021 on the management of glomerular diseases, including C3G.²⁵ KDIGO highlights that an optimal treatment strategy for C3G has not been established, and that current management recommendations are based on expert opinion, retrospective cohort data and extrapolation from other glomerular diseases, as well-controlled data in C3G were unavailable at time of guideline writing.²⁵

KDIGO recommendations as well as information about the use of various treatments in UK clinical practice, based on insights from two advisory boards held by Novartis with UK clinicians in 2022 (nine advisors)²⁶ and 2024 (10 advisors),²⁷ are summarised below in the following sections. An overview of the current treatment pathway for C3G in the UK is presented in Figure 3.

Figure 3: Current treatment pathway for C3G in the UK



^aTo a maximally tolerated licensed dose, unless intolerant or contraindicated. ^bOnly a very small number of patients with highly aggressive post-transplant recurrence of C3G qualify for treatment with eculizumab under the NHS England commissioning policy.²⁸

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C3G, complement 3 glomerulopathy; CS, corticosteroids; MMF, mycophenolate mofetil; NHS, National Health Service; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

1.3.5.1 ACEi/ARB

For the treatment of people with C3G, the international KDIGO 2021 guidelines recommend standard supportive measures as for other glomerular diseases.²⁵ This includes the use of an ACEi or ARB (RAS inhibitors) to a maximally tolerated licensed dose, as initial therapy to reduce proteinuria and manage hypertension.²⁵ Lifestyle modifications, such as optimal nutrition, weight normalisation, regular exercise, and smoking cessation, should be encouraged alongside use of ACEis/ARBs.^{5, 25}

In clinical advisory boards, UK clinicians confirmed that ACEis/ARBs are commonly used in UK clinical practice, in up to 100% of their patients with C3G.^{26, 27} Advisors were aligned that ACEi/ARB treatment was effective in reducing proteinuria and has a favourable safety profile; Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

however, they highlighted that ACEis/ARBs do not alter active glomerular inflammation or affect the underlying complement-mediated disease process in C3G, and are thus unable to prevent disease progression.²⁶

In an international cross-sectional study (Adelphi Disease Specific Programme [DSP]), 90.6% (n=29/32) of patients with C3G from the UK were receiving treatment at the time of survey completion by their nephrologists. Of these, 82.8% (n=24/29) received an ACEi or ARB.⁹⁰

1.3.5.2 Immunosuppression with MMF and/or CS

The KDIGO 2021 guidelines recommend that C3G patients with moderate to severe disease (proteinuria >1 g/day and haematuria or have had declining kidney function for at least 6 months) should be further treated with MMF plus CS.²⁵

Discussion in an advisory board held by Novartis in 2022 highlighted mixed opinions among UK clinicians about the clinical utility of MMF and CS in C3G, with usage of these treatments (in combination or individually) varying across centres.²⁶ Advisors emphasised that the evidence for the use of MMF in C3G was limited and that the KDIGO recommendation was based on observational data only, with clinical effectiveness findings varying between studies.^{25, 26} Views on the effectiveness of CS were similar, although it was suggested that short-term use could be beneficial in some patients for reducing inflammation.²⁶ With both MMF and CS, in addition to limited efficacy evidence in C3G, clinicians considered the risk of gastrointestinal side effects and an increased risk of infection with immunosuppression when determining the benefit-risk profile for individual patients.^{26, 91} CS are also associated with various other side effects including musculoskeletal effects (osteoporosis and myopathy), weight gain, hypertension and insomnia which can be worsened by increased doses and continued administration.⁹² Several UK clinicians reported that they often prefer to enrol patients with C3G in a clinical trial instead of using MMF and/or CS, if a suitable study is available.²⁶

During the 2024 advisory board, clinicians estimated that MMF/CS use in UK clinical practice ranged from 30–70% of patients; while this points to some variation between centres, one advisor also highlighted that estimates may differ depending on whether clinicians considered the proportion of their patients on MMF/CS currently, or at any time during the disease course.²⁷ In the Adelphi DSP, of the UK patients receiving treatment at the time of survey completion, 41.4% (n=12/29) and 37.9% (n=11/29) were receiving treatment with MMF and CS, respectively.⁹⁰

1.3.5.3 SGLT2 inhibitors

Whilst not reflected in the KDIGO 2021 guidelines, following recent licence extensions to patients with CKD, SGLT2is are also increasingly used as part of established clinical management, as supportive background medication alongside ACEis/ARBs.^{26, 27} However, no data are available on the efficacy and safety of SGLT2is specifically in patients with C3G, and UK clinicians noted that SGLT2is would not be used in patients who are on immunosuppression, including transplanted patients.²⁶

1.3.5.4 Eculizumab

The KDIGO 2021 guidelines state that if treatment with MMF plus CS fails, eculizumab should be considered.²⁵ However, in the UK, funding of eculizumab for C3G is restricted by an NHS England Clinical Commissioning Policy, and its use is highly limited.^{26, 28} NHS England commissioning criteria restrict the use of eculizumab to a subset among patients with post-transplant recurrence of C3G, with evidence indicative of highly aggressive disease, for example,

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active glomerulonephritis with cellular crescents on kidney biopsy and a >20% decline in eGFR within the previous three months.^{26, 28} Since the policy was established in 2017, up to March 2023, only 7 UK patients with C3G met the criteria and were able to access eculizumab.³⁶ In the 2024 advisory board, one clinician confirmed that overall still only 8 or 9 patients with C3G had received eculizumab in the UK up to October 2024.²⁷

In addition to access limitations, UK clinicians highlighted that as a terminal complement component 5 (C5) inhibitor, eculizumab does not target the overactivation of the complement alternative pathway which is the root cause of C3G.²⁶ KDIGO also summarises that the benefits of terminal complement blockade with C5 inhibitors remain unestablished in C3G and reports inconsistent efficacy results from small studies,²⁵ which was echoed by UK clinicians based on their clinical experience with eculizumab in a small number of patients with post-transplant recurrent C3G.^{26, 27}

1.3.5.5 Clinical trial enrolment

The KDIGO 2021 guidelines recommend that patients who fail to respond to the outlined treatment approaches should be considered for a clinical trial where available.²⁵ In UK clinical practice, enrolment in a clinical trial is often considered at an earlier stage, given clinicians' concerns with currently available immunosuppressants and the fact that none of the current treatment options address the underlying cause of disease by targeting C3G pathogenesis.^{5, 7, 25-27, 88}

1.3.6 Disease burden and unmet need

1.3.6.1 Clinical burden

Symptoms of C3G, such as oedema and fatigue, can have a noticeable impact on daily activities.^{7-10, 93, 94} Oedema can be intermittent or severe, affecting the ability of people with C3G to carry out physical tasks, such as standing, walking, and climbing stairs.^{7, 94} An international cross-sectional survey among people with C3G and a median eGFR of 50 mL/min/1.73 m² (IQR: 32–70 mL/min/1.73m²) using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire (n=118) found a severe impact of fatigue on all aspects of patients' lives, with over three-quarters of participants reporting that they limit social activities (78%) and need to sleep during the day (77%), and almost half of the participants (47%) feeling too tired to eat, due to their fatigue.⁹⁵ In an international 2017 forum of people with C3G and carers for people with C3G, including representatives from the UK, one participant stated that “the fatigue is overwhelming”.⁷ Fatigue may be further exacerbated in patients with C3G receiving dialysis.⁹⁶ Other symptoms impacting QoL include back/side/abdominal pain, appetite loss, oliguria, and sleeping problems.^{7, 9, 93} Pain/discomfort (at a level of at least ‘slight’) was reported by 65% in an international study of 118 people with C3G completing the EQ-5D-5L questionnaire.⁹⁵ Whilst many people with C3G report a diminished QoL, this is especially true for up to 40% of patients who develop nephrotic syndrome, which is characterised by a high symptom burden and complications associated with increased levels of proteinuria, peripheral oedema, hypoalbuminemia and severe lipidaemia.^{19, 97, 98}

Kidney dysfunction and damage associated with C3G can lead to a number of concomitant conditions and comorbidities including cardiovascular diseases such as hypertension.⁹⁹ Hypertension can increase the risk of diseases such as cardiac disease or stroke, and is a major global cause of premature death in CKD.⁹⁹ Additionally, acquired partial lipodystrophy (APL) and ocular complications such as retinal drusen (yellow deposits under the retina) can occur in

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people with C3G.^{1, 100} People with C3G can also experience periodic episodes of gout, which can lead to joint pain.^{7, 57, 93} Therefore, people with C3G can experience a range of symptoms that can negatively impact their QoL, highlighting the need for effective treatment.

There are currently no targeted treatments for C3G which address the underlying cause of disease, with most treatments prescribed off-label for symptomatic relief.²⁵ The evidence on the efficacy of these treatments in C3G is limited, and some treatments are associated with safety risks and side effects (see Section 1.3.5). With currently available treatments, C3G carries one of the highest risks for irreversible kidney failure of all primary glomerular diseases, with approximately 50% of patients progressing to kidney failure within 10 years of diagnosis, as a result there is a significant unmet need.^{3, 16, 18, 19}

KRT is also associated with significant side effects. Dialysis can be associated with fatigue, hypotension (low blood pressure), itchy skin and muscle cramps.⁹⁶ Kidney transplantation is associated with multiple short-term risks including surgical complications, bleeding, post-transplant infection, and acute rejection of the transplanted kidney.¹⁰¹ The longer-term risks of transplants similarly include infections, organ rejection, and recurrent disease,^{81, 101} which is particularly common in C3G (see Section 1.3.4). Kidney transplant recipients may also experience significant side effects (see Section 1.3.5) and risks associated with long-term use of immunosuppressive regimens to prevent graft rejection, such as increased risk of cancer.^{81, 101-}

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1.3.6.2 Humanistic burden

In addition to symptoms of C3G, the QoL of people with C3G is particularly impacted by the high level of uncertainty around the risk of progression to kidney failure, as well as the current lack of treatment options, which can lead to anxiety and depression.^{7, 93} In the aforementioned 2017 C3G international patient forum, one participant stated that “It’s horrible all around. You know it’s going to get worse” and another noted “what’s most difficult is knowing that time is not on my side...without a viable drug treatment, I know that a healthy diet, exercise, and following doctor’s orders will not stop the progression of this disease...This absolutely frightens me...I can only imagine things getting worse”.⁷ The impact of the disease on mental health is further aggravated by the ultra-rare nature of C3G, with the lack of information available about the disease and symptoms adding to a feeling of helplessness, isolation, and loneliness.^{7, 93} One participant of the 2017 patient forum stated “you feel like you’re going through it alone”, with 34% of attendees reporting they felt others did not understand the experience of living with C3G.⁷ In a UK patient advisory board conducted by Novartis in 2022, participants described how the uncertainty around future progression of C3G limits the choices they have in life, both on a personal and professional level.⁹³ In the 2017 C3G patient forum, one participant summarised their feelings as “We were afraid to travel. We were afraid to make plans. We were afraid to do much of anything”.⁷

Symptoms of the disease, lifestyle and diet restrictions, and dialysis as a very time-consuming treatment, put a burden on daily life for patients and their families and carers.^{7, 93, 104} Young people with C3G report not being able to attend education regularly, impacting their future career opportunities, and feeling stigmatised among peers from having to follow a strictly controlled diet.⁹³ Treatment decisions can also contribute to the psychological burden of the disease, with concerns around kidney transplants and the potential for C3G recurrence resulting in patients feeling as though they must “trade in their current condition for another unknown”.⁷

Overall, QoL in people with C3G is lower than in the general population, with EQ-5D showing impact in particular in the anxiety/depression, pain/discomfort, and usual activities domains.⁹⁵ QoL notably decreases in more advanced stages of CKD, as reported by both C3G patients,⁸ and CKD patients more broadly, with dialysis associated with the lowest utility values.¹⁰⁵

Available carer burden evidence is limited in C3G, although given the substantial symptom burden experienced by patients with C3G (see Section 1.3.6.1), their family and carers may need to provide additional support with daily activities and medical appointments.^{7, 90, 106} The impact on family life was explored in the 2017 C3G patient forum, with participants explaining that “[t]he anxiety is spread throughout an entire family”.⁷

1.3.6.3 Economic burden

Due to the rarity of the condition, there is limited evidence regarding the economic burden of C3G (see Appendix G). A Kidney Research UK report notes that the key driver of the cost of rare kidney diseases, such as C3G, is the need for dialysis or transplants in patients reaching kidney failure.¹⁰⁶ As discussed in Section 1.3.4, the prognosis for many people with C3G is kidney failure, with 50% of patients progressing to kidney failure within 10 years of diagnosis.^{3, 16, 18, 19} Given the early age at diagnosis (median age 21–23 years), rapid disease progression, and high likelihood of post-transplant disease recurrence,^{1, 16} patients are likely to require dialysis for several decades, or multiple transplants over a lifetime which increases the economic burden of C3G. In a recent analysis of prevalent C3G patients in RaDaR, 46% of 240 patients were on KRT (15% on dialysis, 31% transplanted).¹⁷

While there is limited information regarding direct costs for C3G, CKD more broadly places a high economic burden on the NHS, which increases substantially as the disease progresses. For example, the number of minimum routine monitoring checks recommended by NICE increases with CKD stage.¹¹ In 2023, the costs of CKD stages 1–5 prior to initiation of KRT were estimated to be £1.95 billion, with 91% estimated to be attributable to CKD stages 3–5.¹⁰⁶ This highlights the importance of preventing or delaying disease progression in chronic kidney diseases such as C3G.

KRT is a key driver of the high costs associated with CKD, including estimated costs to the NHS in 2023 of £1.05 billion for dialysis, £225 million for dialysis transport costs, and £293 million for transplantations.¹⁰⁶ Most transplant costs are attributable to the procedure itself; however, there are additional costs associated with ongoing care following transplantation and adverse events due to transplantation and organ rejection.¹⁰⁶ Furthermore, whilst patients are waiting for a suitable donor organ, which currently ranges from 2–3 years in the UK, many will require dialysis, leading to further costs to the NHS in the interim.¹⁰⁶ There are also concerns with NHS resource constraints, with dialysis and transplantation services reported to already be operating at maximum capacity.¹⁰⁶ Due to the high rates of disease recurrence and high risk of graft failure in patients with C3G,^{5, 19, 20, 22-24, 83} many patients may need to go back onto chronic dialysis or receive a further kidney transplant, which means that costs associated with KRT may be incurred for prolonged periods of time and/or incurred multiple times. With growing numbers of people requiring dialysis, the demand for dialysis is estimated to require a 400% increase in capacity by 2033, which would place an increased economic burden on the NHS.¹⁰⁶

In addition to the direct costs associated with dialysis, some patients rely on NHS-funded transport for in-centre haemodialysis (HD) (3x per week).^{106, 107} A UK study from Liu et al. 2015 suggests these costs could be significant, costing the NHS approximately £9,600 per in-centre HD patient per year (value inflated to 2022/23; further details are provided in Section 3.5.2).¹⁰⁸

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¹⁰⁹ Transport costs funded by the NHS may be expected to increase, given the NHS' recent universal commitment to supporting patients' transport for in-centre HD sessions through organised transport or financial reimbursement, as outlined in the national eligibility criteria for non-emergency patient transport services (NEPTS).¹¹⁰⁻¹¹²

Indirect costs/productivity losses

C3G is also associated with productivity losses for individuals with C3G and their carers. Dialysis was estimated in 2023 to cost the UK economy £372 million due to lost patient and carer productivity (missed work time), and this is expected to increase in the next decade.¹⁰⁶ In an international study using the Work Productivity and Activity Impairment (WPAI) questionnaire, people with C3G reported a mean overall work impairment score of 47.7%, with an impairment at work score of 43.8% and work time missed reported as 17.6%, due to their C3G (where 100% represents being completely prevented from undertaking work).⁹⁰ In the international 2017 patient forum of individuals with C3G, 25% of respondents reported that they had missed school or work due to C3G.⁷

1.3.6.4 Unmet need

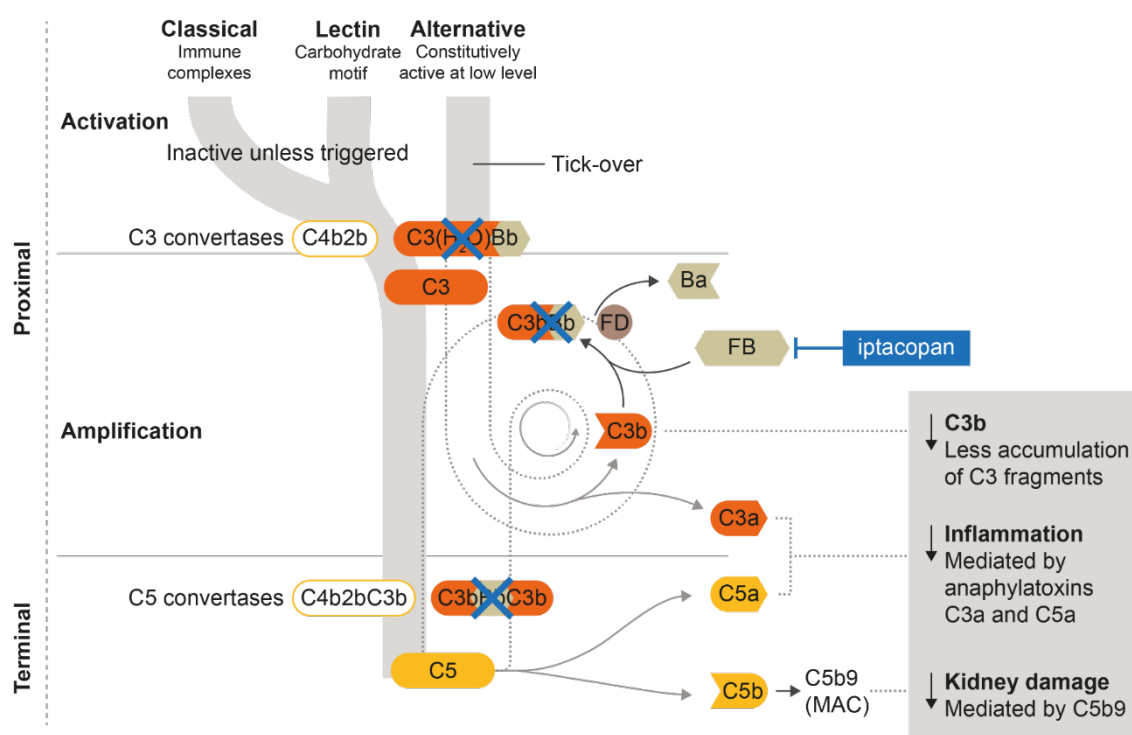
There are currently no approved targeted therapies for C3G. Treatments that are used have limited efficacy in C3G, and around 50% of patients progress to kidney failure within 10 years of diagnosis.^{3, 16, 18, 19} Once someone has progressed to kidney failure, they require lifelong dialysis or a kidney transplant.^{7, 48} Kidney transplantation is not curative, however, and there is a high rate of C3G recurrence post-transplant (55–85%).^{5, 19, 22-24, 83, 113}

There is therefore a high unmet need in C3G. UK clinicians participating in advisory boards conducted by Novartis described the current unmet need in C3G as “huge” and “enormous” and highlighted the need for novel targeted therapies in C3G.^{26, 27} Clinical and patient organisations further attested to this unmet need in their responses to the draft scope consultation of iptacopan for C3G.¹⁰⁴

1.3.7 Proposed positioning of iptacopan

In C3G, overactivation of the complement alternative pathway leads to deposition of C3 within the glomeruli, triggering inflammation and glomerular injury.⁴⁸ Iptacopan is an oral, first-in-class, proximal complement inhibitor that specifically binds Factor B (Figure 4). This selectively blocks alternative pathway overactivation by inhibiting alternative pathway-related C3 convertase activity, leading to decreased cleavage of C3 and reduced C3 deposition in the kidney.³⁷ Iptacopan is expected to be the first targeted treatment which addresses the underlying pathophysiology of C3G.

Figure 4: Iptacopan mechanism of action



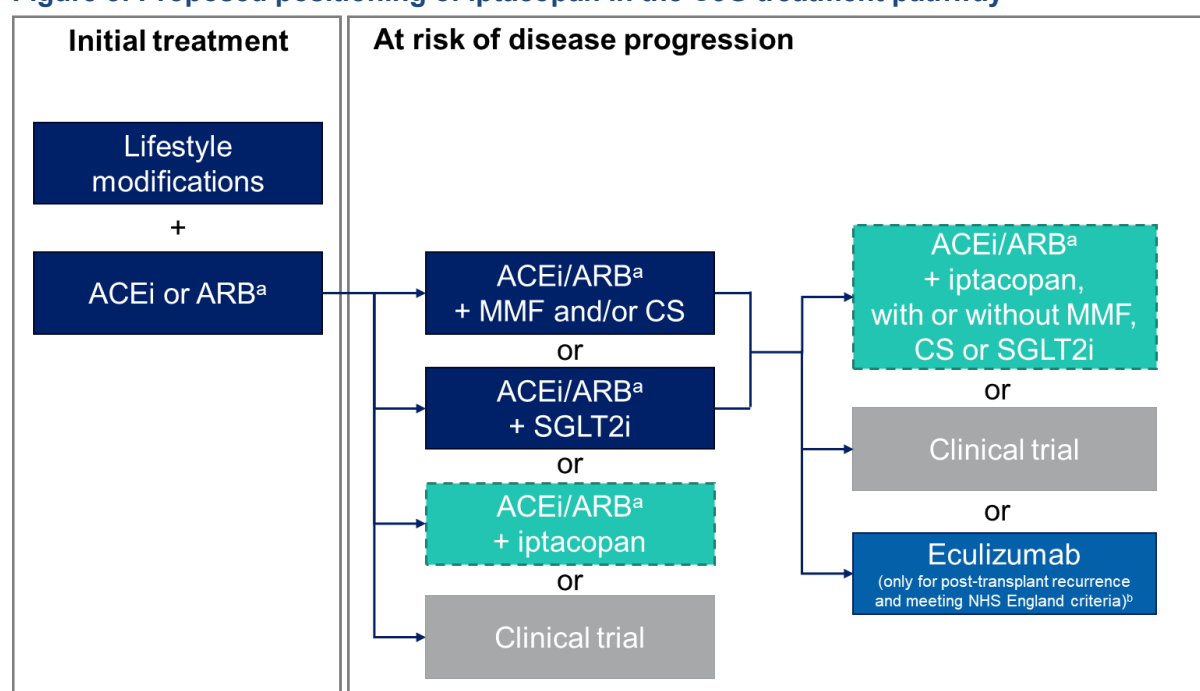
Abbreviations: C3, complement component 3; C5, complement component 5; FB, Factor B; FD, Factor D; FH, Factor H; FI, Factor I; MAC, membrane attack complex

Sources: Adapted from Bomback et al. 2022,⁴⁸ and Keir et al. 2012.⁵⁵

In recognition of the high unmet need in C3G and the potential of iptacopan, as the first targeted treatment for C3G, to offer significant additional benefit, iptacopan has been awarded several designations. This includes an Innovation Passport under the UK Innovative Licensing and Access Pathway (ILAP)¹¹⁴ and a [REDACTED], as well as an orphan drug designation¹¹⁶ and a Priority Medicines (PRIME) designation¹¹⁷ from the EMA. Clinicians' expectation that iptacopan will offer significant additional benefit to patients with C3G²⁷ is also evidenced by [REDACTED]

It is anticipated that iptacopan will be licensed for the treatment of adult patients with C3G in combination with a RAS inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated.³⁰ A summary of the proposed positioning of iptacopan in the C3G treatment pathway is shown in Figure 5. It is expected that iptacopan would be used in combination with a maximally tolerated dose of an ACEi or ARB (unless intolerant or contraindicated), in line with the design of the clinical trials and the anticipated indication wording, in patients who remain at risk of disease progression. This may also include use of iptacopan in combination with ACEi/ARB and MMF and/or CS, or an SGLT2i. In the iptacopan clinical trials in C3G (see Section 2.4.1 and Section 2.5.1), patients on a stable dose of MMF and/or CS, or SGLT2i were eligible for enrolment, with all medications maintained on a stable dose during the trial.⁴⁸

Figure 5: Proposed positioning of iptacopan in the C3G treatment pathway



^aTo a maximally tolerated licensed dose, unless intolerant or contraindicated. ^bOnly a very small number of patients with highly aggressive post-transplant recurrence of C3G qualify for treatment with eculizumab under the NHS England commissioning policy.²⁸

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C3G, complement 3 glomerulopathy; CS, corticosteroids; MMF, mycophenolate mofetil; NHS, National Health Service; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

1.4 Equality considerations

Novartis supports access to treatment for all people with C3G regardless of their age, ethnicity and socioeconomic background. While the currently available iptacopan clinical trial results and expected licensed indication are limited to adults, Novartis is committed to pursuing a licence extension and access to iptacopan for younger people with C3G as soon as the available evidence permits.

Average wait time for adults in the UK to receive a kidney transplant is currently 2-3 years.¹⁰⁶ However, the 2023–2024 NHS Blood and Transplant annual report on ethnicity differences in organ donation and transplantation and a Kidney Research UK report from 2023 both highlight that there is considerable inequality across ethnic groups with regards to CKD and access to kidney transplants, with individuals of Black and Asian descent more likely to be diagnosed later, progress faster towards kidney failure and face much lengthier wait times for transplants compared with white people.^{106, 118} Socio-economic deprivation is also correlated with poor survival outcomes in CKD, with people who are socio-economically deprived experiencing faster rates of disease progression, a higher risk of cardiovascular disease and premature mortality.¹⁰⁶ Socio-economic deprivation is also associated with lengthier wait times for transplants and limited access to living donor transplants, leading to higher rates of long-term kidney failure and mortality.¹⁰⁶

People with C3G face an inherent level of health inequalities due to the ultra-rare nature of the disease which leads to significant disparities in healthcare access and outcomes, when compared to more common conditions. Robust evidence generation for new medicines is challenging in ultra-rare diseases, with small patient populations restricting the ability to conduct large-scale clinical trials. Small sample sizes in clinical trials further result in challenges in health technology assessments (HTAs) due to the resulting higher degree of uncertainty in the available evidence. Consequently, this may limit the availability of effective treatment options for people with ultra-rare diseases. Lack of awareness and education about ultra-rare diseases, including among healthcare professionals, further exacerbates health inequalities when compared to more common conditions, due to delays in diagnosis, absence of evidence-based care pathways, and variation in service provision across different parts of the country.¹¹⁹⁻¹²¹

The NICE Prioritisation Board confirmed that iptacopan for C3G meets the Highly Specialised Technologies (HST) routing criteria that relate to rarity of the disease (routing criteria 1 and 2).¹²² While the NICE evaluation takes place using the Single Technology Appraisal (STA) route, NICE are asked to apply flexibility in the STA process for iptacopan for C3G to enable timely and equitable access for people with an ultra-rare disease of this nature, when compared to treatments being assessed through the STA process for conditions with a much higher prevalence.

2 Clinical effectiveness

The main clinical evidence base for iptacopan as an add-on treatment to standard of care (SoC) in adult patients with C3G is informed by the APPEAR-C3G trial, with supportive evidence from the Phase 2 study and an open-label extension study

- APPEAR-C3G (NCT04817618)³² is an international, multicentre, randomised, double-blind, parallel group, placebo-controlled Phase 3 study to evaluate the efficacy and safety of iptacopan in patients with native kidney C3G (N=74)
- The Phase 2 study (NCT03832114)¹²³ was an international, multicentre, open-label, single-arm, non-randomised study in adults with native kidney or post-transplant recurrent C3G (N=27)
- The open-label extension study (NCT03955445)³⁵ is an ongoing non-randomised study in patients receiving iptacopan after completing treatment in APPEAR-C3G or the Phase 2 study

Clinical evidence demonstrated the efficacy of iptacopan in adult patients with C3G

- APPEAR-C3G met its primary endpoint with iptacopan treatment resulting in a statistically significant and clinically meaningful reduction in 24h UPCR by 35.1% (95% CI: 13.8%, 51.1%; p=0.0014) following 6 months of treatment with iptacopan compared with placebo on top of optimised background therapy³³
- The change in eGFR in APPEAR-C3G supported the treatment effect of iptacopan, with a change from baseline to 6 months of 2.16 mL/min/1.73m² (95% CI: -2.75, 7.06; multiplicity-adjusted 1-sided p-value: 0.3241), as measured by the adjusted mean difference of iptacopan versus placebo (secondary endpoint)³³
- An exploratory endpoint assessed the change in eGFR slope, comparing the rate of change of eGFR following initiation of iptacopan with patients' eGFR trajectory prior to iptacopan treatment. Patients included in APPEAR-C3G showed a rapid decline in eGFR prior to starting iptacopan treatment, with an eGFR slope of -7.22 mL/min/1.73 m²/year (95% CI: -10.10, -4.35; estimated based on up to 2.5 years of pre-iptacopan data). Treatment with iptacopan (including longer-term follow-up data from the extension study, with up to 2 years treatment duration) led to stabilisation of the eGFR decline, with the on-iptacopan slope estimated as -0.29 mL/min/1.73m²/year (95% CI: -3.88, 3.31). This equated to a change in annual eGFR slope of 6.94 mL/min/1.73m² (95% CI: 3.48, 10.39; p=0.0001) compared with pre-iptacopan treatment¹²⁴

Iptacopan was well-tolerated; AEs were balanced between the iptacopan and placebo arms during the controlled double-blind period of APPEAR-C3G (controlled safety set)

- The safety profile of iptacopan was well characterised in the clinical trials. In APPEAR-C3G, iptacopan was well tolerated, with the majority of AEs being mild or moderate in severity^{33, 125}
- In the broad safety set, including data from all patients receiving at least one dose of iptacopan 200 mg b.i.d. in the treatment periods of all three studies (N=101), 36 serious adverse events (SAEs) were experienced by 19.8% of patients; approximately half of these were infection-related.¹²⁵ Three patients discontinued iptacopan due to AEs (all discontinuations occurred during the ongoing open-label extension study), with all three due to SAEs determined not to be related to iptacopan¹²⁵

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in October–December 2021, and subsequently updated in October 2024, to identify relevant clinical trial evidence on the efficacy and safety of treatments for patients with C3G. The SLR scope was broad, including both randomised and non-randomised clinical trials in patients diagnosed with C3G, and receiving any intervention for C3G (including investigational treatments, best supportive care or placebo).

Across the original SLR and its update, 33 publications reporting on 15 unique studies were included. Of these, 2 studies included patients with C3G who were treated with iptacopan (in the SLR, categorised as APPEAR-C3G and the Phase 2 trial, with open-label extension study results for patients originating from the Phase 2 trial included as linked publications for the Phase 2 trial).

Full details of the process and methods used in the SLR, as well as a description of the included studies and results, are provided in Appendix B.

2.2 List of relevant clinical effectiveness evidence

As identified by the SLR, the primary source of clinical efficacy evidence for iptacopan in C3G is the Phase 3 trial APPEAR-C3G. Supportive evidence is provided by the Phase 2 trial, and an open-label extension study including patients who completed either the Phase 2 trial or APPEAR-C3G. An overview of these studies is provided in Table 4.^{33, 37, 38, 126} The clinical SLR did not identify any other studies for iptacopan in the relevant patient population as defined by the NICE final scope.

Table 4: Clinical effectiveness evidence for iptacopan in C3G

Study	APPEAR-C3G (NCT04817618) ^{32, 33, 126}	Phase 2 (NCT03832114) ^{37, 123}	Open-label extension study (NCT03955445) ^{35, 38}
Study design	Multicentre, randomised, double-blind, parallel group, placebo-controlled, pivotal Phase 3 study	Multicentre, open-label, single-arm, non-randomised Phase 2 study	Multicentre, open-label, non-randomised extension study
Population	Adult patients aged 18–60 years ^a with biopsy-confirmed native kidney C3G	Adult patients aged 18 years or older, with biopsy-confirmed native kidney C3G (native kidney cohort) or recurrent C3G post kidney transplant (post-transplant recurrent cohort)	Patients who completed the APPEAR-C3G or Phase 2 studies ^b
Intervention	Iptacopan 200 mg b.i.d.	- Weeks 1–4: iptacopan dose escalation from 10 mg (Week 1), 25 mg (Week 2), 100 mg (Week 3) to 200 mg (Week 4), b.i.d. - Weeks 5–12: 200 mg b.i.d.	Iptacopan 200 mg b.i.d.
Comparator	Placebo (during 6-month double-blind treatment period, before transition to 6-month open-label	N/A	N/A

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Study	APPEAR-C3G (NCT04817618) ^{32, 33, 126}	Phase 2 (NCT03832114) ^{37, 123}	Open-label extension study (NCT03955445) ^{35, 38}
	treatment with iptacopan 200 mg b.i.d.)		
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	Yes
Rationale if study not used in model	N/A	N/A	N/A
Reported outcomes specified in the decision problem	- Proteinuria (Change from baseline [CfB] in UPCR) - Kidney function (CfB in eGFR, composite renal endpoint, eGFR slope) - Health-related quality of life (patient reported outcomes: FACIT-Fatigue score) - Adverse effects of treatment	- Proteinuria (CfB in UPCR) - Kidney function (CfB in eGFR, eGFR slope) - Adverse effects of treatment	- Proteinuria (CfB in UPCR) - Kidney function (change in eGFR, composite renal endpoint, eGFR slope) - Adverse effects of treatment
All other reported outcomes	- Histological endpoints (glomerular C3 deposit scores, histologic total activity scores) - Circulating biomarker levels (including serum C3, AP activity, plasma Bb, plasma sC5b-9 and urinary sC5b-9/creatinine)	Histological endpoint (glomerular C3 deposit scores)	Histological endpoint (glomerular C3 deposit scores)

^aA separate and independent cohort of adolescent patients (aged 12–17 years) with C3G was initiated later in the APPEAR-C3G study. The adolescent cohort will read out at a later date; this patient population has not been included in the initial licence application for C3G and will not be considered in this submission. ^bThis is also an extension study for a Phase 3 study investigating the efficacy and safety of iptacopan in patients with idiopathic immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN; NCT05755386)¹²⁷.

Abbreviations: b.i.d., twice daily; C3, complement 3; C3G, complement 3 glomerulopathy; CfB, change from baseline; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; N/A, not applicable; UPCR, urine protein-to-creatinine ratio.

Sources: Kavanagh et al. Oral. Presented at ERA Congress 2024;¹ Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data);² Wong et al. 2023;³⁷ Novartis Data on File. 2024 (Open-label extension study clinical study report; 36-month interim analysis);³⁸ ClinicalTrials.gov (NCT04817618);³² ClinicalTrials.gov (NCT03832114);¹²³ ClinicalTrials.gov (NCT03955445).³⁵

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2.3 Critical appraisal of the relevant clinical effectiveness evidence

APPEAR-C3G was quality assessed using the Cochrane Risk of Bias 2 tool, while the single-arm Phase 2 trial was assessed using the Cochrane Risk of Bias In Non-Randomized Studies (ROBINS-I) tool.^{128, 129} APPEAR-C3G was determined to be at low risk of bias, while the Phase 2 trial was considered to be associated with a moderate risk of bias. Further details are provided in Appendix B.

2.4 APPEAR-C3G

2.4.1 Summary of methodology

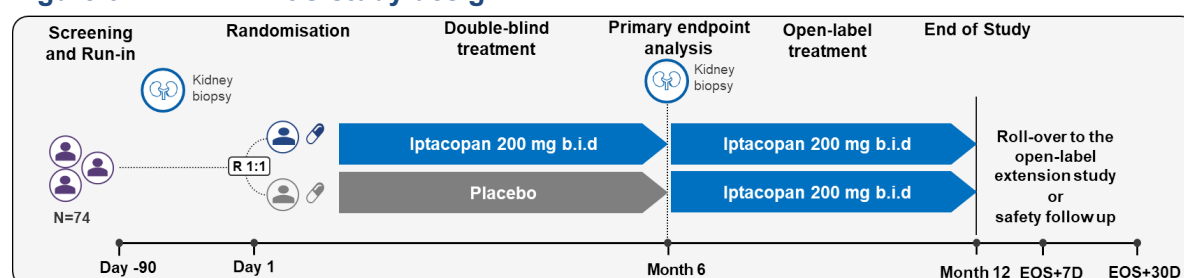
APPEAR-C3G (NCT04817618) is an international, multicentre, randomised, double-blind, parallel group, placebo-controlled Phase 3 study to evaluate the efficacy and safety of iptacopan in patients with native kidney C3G.^{32, 33, 48, 126}

The APPEAR-C3G trial comprised the following three periods (Figure 6):³³

- A screening/run-in period lasting up to 90 days
- A 6-month double-blind treatment period, during which patients received blinded treatment with 200 mg iptacopan or placebo orally b.i.d. (randomisation 1:1)
- A 6-month open-label treatment period, during which all patients received open-label iptacopan 200 mg orally b.i.d.

Following completion of study treatment at 12 months, patients were given the option to discontinue iptacopan treatment and enter a 30-day safety follow-up period or continue iptacopan treatment by transitioning to a roll-over open-label extension study (further information on the open-label extension study is provided in Section 2.5.2).³³

Figure 6: APPEAR-C3G study design



Abbreviations: b.i.d., twice daily; C3G, complement 3 glomerulopathy; D, day; EOS, end of study; N, total number of patients; R, randomisation.

Sources: Bombback et al. 2022;⁴⁸ Nester et al. Oral. Presented at ASN 2024.¹³⁰

This submission only considers the adult cohort of the trial, in line with the patient population described in the decision problem and as included in the initial licence application for iptacopan in C3G. A separate and independent cohort of adolescent patients (aged 12–17 years) was initiated later in the study and will read out at a later date;³² this cohort will not be considered in this submission.

A summary of the methodology of the APPEAR-C3G trial is provided in Table 5.

Table 5: Summary of methodology: APPEAR-C3G

Parameter	APPEAR-C3G (NCT04817618)
Study design	Multicentre, randomised, double-blind, parallel group, placebo-controlled Phase 3 study
Location	79 sites across 18 countries: United Kingdom (3 sites; 9 adult patients), Argentina, Brazil, Canada, China, Czechia, France, Germany, Greece, India, Israel, Italy, Japan, the Netherlands, Spain, Switzerland, Turkey, and the US
Key eligibility criteria for patients	Key inclusion criteria: - Adult patients, 18–60 years of age^a - Diagnosis of C3G as confirmed by kidney biopsy within 12 months prior to enrolment - On maximally recommended or tolerated dose of ACEi or ARB for at least 90 days prior to randomisation - Mycophenolic acid (MPA)^b, corticosteroids (CS; prednisolone ≤7.5 mg/day or equivalent), SGLT2is and mineralocorticoid receptor antagonists (MRAs) were allowed if maintained on a stable dose for at least 90 days prior to randomisation - UPCR ≥1.0 g/g (≥113 mg/mmol) sampled from the first morning void urine sample at Day -75 and Day -15 - eGFR (using the CKD-EPI formula)¹³¹ or measured eGFR ≥30 mL/min/1.73m² at screening and Day -15 - Reduced serum C3 (<0.85x lower limit of the central laboratory normal range, i.e. <77 mg/dL) at screening - Vaccination against <i>N. meningitidis</i>, <i>S. pneumoniae</i> (mandatory) and <i>H. influenzae</i> (recommended) if not previously vaccinated or if a booster was required Key exclusion criteria: - Solid organ (including kidney) or cell transplant - Rapidly progressive crescentic glomerulonephritis^c - Kidney biopsy showing interstitial fibrosis/tubular atrophy of >50% - Monoclonal gammopathy of undetermined significance^d Detailed inclusion and exclusion criteria for APPEAR-C3G can be found in Appendix J
Trial drug(s)	Patients were randomised 1:1, stratified by CS and/or MPA treatment at randomisation (yes versus no), to receive either: Intervention: Iptacopan (LNP023) 200 mg b.i.d. (oral capsules) for 6 months (double-blind) followed by open-label iptacopan 200 mg b.i.d. for an additional 6 months, N=38 OR: Comparator: Placebo b.i.d. (oral capsules) for 6 months (double-blind) followed by open-label iptacopan 200 mg b.i.d. for 6 months, N=36 Both iptacopan and placebo were administered on top of optimised background therapy, including ACEis/ARBs at a maximally tolerated dose, with or without CS and/or MPA or SLGT2is, provided these therapies were maintained at a stable dose for at least 90 days prior to randomisation. The following medications were prohibited during the treatment period: cyclophosphamide, calcineurin inhibitors, eculizumab, rituximab, other

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Parameter	APPEAR-C3G (NCT04817618)
	standard immunosuppressant therapies (except MMF, mycophenolate sodium [MPS] and CS at a dose of prednisolone ≤ 7.5 mg/day or equivalent), and live vaccines.
Primary endpoint(s)^e	Double-blind (6-month) treatment period – iptacopan versus placebo: - Log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine collection) at 6 months 12-month treatment period: - CfB in log-transformed UPCR at the 12-month visit (both treatment arms) - Change in log-transformed UPCR from the 6-month visit to the 12-month visit (placebo-iptacopan switch arm only)
Secondary endpoints^e	Double-blind (6-month) treatment period – iptacopan versus placebo: - CfB in eGFR at 6 months - Proportion of patients achieving the composite renal endpoint ($\geq 50\%$ reduction in UPCR + $\leq 15\%$ reduction in eGFR compared to the baseline visit) at 6 months - CfB in disease total activity score in a kidney biopsy at 6 months - CfB in the FACIT-Fatigue score at 6 months - Safety and tolerability 12-month treatment period: - Proportion of patients achieving the composite renal endpoint ($\geq 50\%$ reduction UPCR + $\leq 15\%$ reduction in eGFR) compared to the baseline visit at 12 months (both treatment arms) and compared to the 6-month visit at 12 months (placebo-iptacopan switch arm only) - CfB in the total activity score in a kidney biopsy at 12 months (both treatment arms) and change from the 6-month visit to the 12-month visit (placebo-iptacopan switch arm only) - CfB in the FACIT-Fatigue score at 12 months (both treatment arms) and change from the 6-month visit to the 12-month visit (placebo-iptacopan switch arm only) - Safety and tolerability
Key exploratory endpoints^d	Double-blind (6-month) treatment period – iptacopan versus placebo: - CfB in glomerular C3 deposit scores from a kidney biopsy at 6 months - CfB in circulating biomarker levels, including serum C3, AP activity, plasma Bb, plasma sC5b-9 and urinary sC5b-9/creatinine, at 6 months 12-month treatment period: - CfB in eGFR at 12 months (both treatment arms) - Change in eGFR from the 6-month visit to the 12-month visit (placebo-iptacopan switch arm only) - Change in eGFR slope - CfB in glomerular C3 deposit scores from a renal biopsy at 12 months A list of all exploratory endpoints assessed in APPEAR-C3G can be found in Appendix J
Pre-planned subgroup analyses of primary endpoint	The subgroup analysis included: - Age group - Sex - Race - Region - CS and/or MPA at randomisation (yes versus no) - Baseline UPCR (< 3 g/g versus ≥ 3 g/g)

Parameter	APPEAR-C3G (NCT04817618)
	- Baseline total urinary protein (<3 g/day versus ≥3 g/day) - Baseline eGFR (<60 mL/min/1.73m² versus ≥60 mL/min/1.73m² and <90 mL/min/1.73m² versus ≥90 mL/min/1.73m²) - Baseline C3 (<45 mg/dL versus ≥45 mg/dL) - Years since C3G diagnosis (<2 years versus ≥2 years) - Age at C3G diagnosis (<18 years versus ≥18 years) - C3G disease subtype at diagnosis (C3GN versus DDD) - Hypertension (yes versus no)

^aA separate and independent cohort of adolescent patients (aged 12–17 years) with C3G was initiated later in the APPEAR-C3G study. The adolescent cohort will read out at a later date; this patient population has not been included in the initial licence application for C3G and will not be considered in this submission. ^bMPAs such as MMF or MPS. ^cDefined as a 50% decline in eGFR within 3 months with kidney biopsy findings of glomerular crescent formation seen in at least 50% of glomeruli. ^dConfirmed by the measurement of serum free light chains or other investigation as per local standard of care. ^eCentral laboratory testing was used for all analysis of clinical chemistry and haematology specimens, as well as urinalysis

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; b.i.d., twice daily; C3, complement 3; C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; CS, corticosteroid; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPS, mycophenolate sodium; MRA, mineralocorticoid receptor antagonist; RCT, randomised clinical trial; SGLT2i, sodium-glucose co-transporter 2 inhibitor; UK, United Kingdom; UPCR, urine protein-to-creatinine ratio; US, United States.

Sources: Bombback et al. 2022;⁴⁸ ClinicalTrials.gov (NCT04817618);³² Kavanagh et al. Oral. Presented at ERA 2024.¹²⁶; Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data);³³ Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy).¹²⁴

2.4.1.1 Patient disposition

In APPEAR-C3G, a total of 74 patients were enrolled in the adult cohort, with 38 patients randomised to the iptacopan arm and 36 randomised to the placebo arm. Patient disposition for the double-blind and open-label periods are presented in Table 6. All 74 patients completed the 6-month double-blind period. However, two patients in the iptacopan arm discontinued double-blind treatment due to patient decision and a technical issue. Both of these patients continued double-blind study visits (without treatment) until the end of the double-blind period, and then transitioned to the open-label period where they attended study visits and received open-label iptacopan.³³

Overall, 73 of the 74 patients completed the full 12 months of the study (6 months double-blind period plus 6 months open-label period). One patient originally randomised to the placebo arm discontinued treatment during the open-label period, with the reason recorded as patient decision, was subsequently lost to follow-up and discontinued from the study.³³

Table 6: Participant disposition (full analysis set [FAS])

	Iptacopan (N=38)	Placebo (N=36)	Total (N=74)
Treated, n (%)	38 (100.0)	36 (100.0)	74 (100.0)
Not treated, n (%)	0	0	0
Completed double-blind treatment, n (%)	36 (94.7)	36 (100.0)	72 (97.3)
Completed double-blind period, n (%)	38 (100.0)	36 (100.0)	74 (100.0)
Discontinued from double-blind treatment, n (%)	2 (5.3)	0	2 (2.7)
Discontinued due to subject decision, n (%)	1 (2.6)	0	1 (1.4)

	Iptacopan (N=38)	Placebo (N=36)	Total (N=74)
Discontinued due to technical problems, n (%)	1 (2.6)	0	1 (1.4)
Completed double-blind period, n (%)	38 (100.0)	36 (100.0)	74 (100.0)
Completed open-label treatment, n (%)	38 (100.0)	35 (97.2)	73 (98.6)
Discontinued from open-label treatment, n (%)	0	1 (2.8)	1 (1.4)
Discontinued due to subject decision, n (%)	0	1 (2.8)	1 (1.4)
Completed study, n (%)	38 (100.0)	35 (97.2)	73 (98.6)
Discontinued study, n (%)	0	1 (2.8)	1 (1.4)
Discontinued as lost to follow-up, n (%)	0	1 (2.8)	1 (1.4)

Abbreviations: FAS, full analysis set

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 10-1).³³

2.4.1.2 Baseline demographics and disease characteristics

Patient demographics and disease characteristics at baseline are summarised in Table 7. Of the 74 patients enrolled in the study, 47 were male (63.5%) and 27 were female (36.5%). The majority of patients were of White race (68.9%) and from study sites in Europe (55.4%). The mean (SD) age of all patients was 27.9 (10.7) years.³³

The 74 patients enrolled in the study represent a C3G population at high risk of disease progression based on a mean (SD) 24h UPCR of 3.40 (2.07) g/g or 384.41 (233.46) g/mol at baseline. A high proportion of patients had nephrotic range proteinuria (24h UPCR $\geq$ 3 g/g, 43.2%). Mean (SD) eGFR at baseline was well preserved at 94.1 (31.6) mL/min/1.73m², and systolic and diastolic blood pressures were well controlled.³³

The treatment arms were generally balanced; however, there were imbalances between groups in some baseline disease characteristics such as UPCR, eGFR, and C3G subtype (Table 7). Patients randomised to the iptacopan arm had notably higher UPCR and lower eGFR at baseline, compared with those from the placebo arm. Furthermore, there were a greater number of participants with baseline nephrotic range proteinuria ($\geq$ 3 g/g) in the iptacopan arm (55.3%) than in the placebo arm (30.6%; Table 7).³³

Table 7: APPEAR-C3G baseline demographics and disease characteristics (FAS)

	Iptacopan (N=38)	Placebo (N=36)	Total (N=74)
Baseline demographics			
Age (years)			
Mean (SD)	26.1 (10.39)	29.8 (10.79)	27.9 (10.68)
Gender, n (%)			
Male	27 (71.1)	20 (55.6)	47 (63.5)
Female	11 (28.9)	16 (44.4)	27 (36.5)
Race, n (%)			
White	27 (71.1)	24 (66.7)	51 (68.9)
Black or African American	1 (2.6)	1 (2.8)	2 (2.7)
Asian	9 (23.7)	9 (25.0)	18 (24.3)

Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

	Iptacopan (N=38)	Placebo (N=36)	Total (N=74)
American Indian or Alaska Native	0	1 (2.8)	1 (1.4)
Multiple	0	1 (2.8)	1 (1.4)
Unknown	1 (2.6)	0	1 (1.4)
Region, n (%)			
North America	7 (18.4)	8 (22.2)	15 (20.3)
Europe	22 (57.9)	19 (52.8)	41 (55.4)
Other	9 (23.7)	9 (25.0)	18 (24.3)
Baseline disease characteristics			
Baseline UPCR 24h (g/mol)			
Arithmetic mean (SD)	434.92 (258.529)	331.09 (193.208)	384.41 (233.462)
Geometric mean (95% CI)	376.20 (315.631–448.399)	291.30 (246.127–344.765)	332.19 (293.856–375.519)
Baseline UPCR 24h [g/g]			
Arithmetic mean (SD)	3.85 (2.288)	2.93 (1.710)	3.40 (2.066)
Geometric mean (95% CI)	3.33 (2.793–3.968)	2.58 (2.178–3.051)	2.94 (2.600–3.323)
Baseline UPCR (24h), n (%)			
<339 g/mol [3 g/g]	17 (44.7)	25 (69.4)	42 (56.8)
≥339 g/mol [3 g/g]	21 (55.3)	11 (30.6)	32 (43.2)
Baseline eGFR [mL/min/1.73m²]			
Mean (SD)	89.30 (35.198)	99.22 (26.880)	94.12 (31.612)
Baseline eGFR, n (%)			
<90 mL/min/1.73m ²	19 (50.0)	12 (33.3)	31 (41.9)
≥90 mL/min/1.73m ²	19 (50.0)	24 (66.7)	43 (58.1)
Baseline eGFR, n (%)			
<60 mL/min/1.73m ²	10 (26.3)	4 (11.1)	14 (18.9)
≥60 mL/min/1.73m ²	28 (73.7)	32 (88.9)	60 (81.1)
Baseline C3 [mg/L]			
Arithmetic mean (SD)	316.8 (243.41)	339.3 (227.96)	327.8 (234.68)
Geometric mean (95% CI)	219.5 (160.09–300.99)	250.0 (184.39–338.88)	233.8 (188.64–289.86)
Baseline C3, n (%)			
<450 mg/L	28 (73.7)	26 (72.2)	54 (73.0)
≥450 mg/L	10 (26.3)	10 (27.8)	20 (27.0)
Hypertension^a, n (%)			
Yes	23 (60.5)	18 (50.0)	41 (55.4)
No	15 (39.5)	18 (50.0)	33 (44.6)
Age at C3G diagnosis, years			
Mean (SD)	22.0 (10.88)	25.3 (10.80)	23.6 (10.90)
Age at C3G diagnosis, n (%)			
<18 years	15 (39.5)	6 (16.7)	21 (28.4)
≥18 years	23 (60.5)	30 (83.3)	53 (71.6)

	Iptacopan (N=38)	Placebo (N=36)	Total (N=74)
Time since first C3G diagnosis, years Mean (SD)	4.60 (4.443)	4.82 (6.046)	4.71 (5.248)
Time since first C3G diagnosis, n (%) <2 years ≥2 years	15 (39.5) 23 (60.5)	15 (41.7) 21 (58.3)	30 (40.5) 44 (59.5)
C3G subtype at diagnosis, n (%) C3GN DDD Mixed C3GN/DDD Unknown	26 (68.4) 9 (23.7) 2 (5.3) 1 (2.6)	32 (88.9) 1 (2.8) 2 (5.6) 1 (2.8)	58 (78.4) 10 (13.5) 4 (5.4) 2 (2.7)

Baseline 24h UPCR refers to UPCR as measured by the geometric mean of two 24h urine collections at baseline/Day 1. Baseline total urinary protein 24h refers to total urinary protein as measured by the geometric mean of two 24h urine collections at baseline/Day 1. Baseline eGFR was defined as the arithmetic mean of two eGFR values at Day -15 visit and Day 1 visit. ^aHypertension is defined based on "hypertension at diagnosis" from C3G medical history and the reported hypertension terms from the medical history.

Abbreviations: C3, complement 3; C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; CI, confidence interval; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set; RAS, renin angiotensin system; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Tables 10-3, 10-4, 10-5 and 10-8).³³

2.4.1.3 Concomitant therapies

All participants were required to be on a stable, maximally recommended or tolerated dose of an ACEi/ARB for the 90-day Screening period and during the study. Patients who received a stable dose of MPA, lower-dose CS (prednisolone ≤7.5 mg/day or equivalent) or SGLT2is were eligible for enrolment and continued these treatments on the same dose during the study. Changes in dose of concomitant therapies were allowed if indicated due to an AE or other safety issue.³³

Overall, 37 participants (97.4%) in the iptacopan arm and 36 participants (100%) in the placebo arm received at least one concomitant medication affecting proteinuria during the double-blind period. The most common concomitant medications received by participants in both arms were RAS inhibitors (iptacopan: 37 participants, 97.4%; placebo: 36 participants, 100%). Therefore, all but one participant, who was intolerant to ACEis/ARBs, received background RAS inhibitor therapy. Additionally, 44.6% of patients received CS and/or MPAs and 5.4% of patients received SGLT2is. A summary of concomitant therapies relevant to C3G is presented in Table 8.³³

Table 8: C3G relevant classes of concomitant medications at randomisation (FAS)

Category of medication	Iptacopan N=38 n (%)	Placebo N=36 n (%)	Total N=74 n (%)
RAS inhibitors/MRA	37 (97.4)	36 (100)	73 (98.6)
RAS inhibitors	37 (97.4)	36 (100)	73 (98.6)
ACEi	19 (50.0)	16 (44.4)	35 (47.3)
ARB	19 (50.0)	20 (55.6)	39 (52.7)
Renin inhibitors	1 (2.6)	1 (2.8)	2 (2.7)
MRA	1 (2.6)	1 (2.8)	2 (2.7)
CS and/or MPA ^a	16 (42.1)	17 (47.2)	33 (44.6)
MPA ^a	14 (36.8)	13 (36.1)	27 (36.5)
CS (systemic)	11 (28.9)	13 (36.1)	24 (32.4)
SGLT2i	2 (5.3)	2 (5.6)	4 (5.4)

^aMPAs such as MMF or MPS.

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; C3G, complement 3 glomerulopathy; CS, corticosteroid; FAS, full analysis set; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPS, mycophenolate sodium; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 10-4 and Table 10-8).³³

2.4.2 Statistical analysis and definition of study groups

A summary of analysis sets and statistical analysis methods for APPEAR-C3G is provided in Table 9.

Table 9: Summary of statistical analyses in APPEAR-C3G

APPEAR-C3G	Description
Analysis sets	• Screening set (SCR): included all patients screened during the study • Randomised analysis set (RAS): included all randomised patients • FAS: included all patients to whom study treatment was assigned by randomisation. According to the intent-to-treat principle, patients were analysed according to the treatment they were assigned to, considering the actual CS and/or MPA use at randomisation (stratification factor) ○ The FAS was used for the primary analysis of the double-blind period, and for efficacy analyses where the entire data from the double-blind period and the open-label period of all patients were used. The FAS excluded any patients without a randomisation number and those who were mis-randomised • Combined full analysis set (CFAS): included all patients randomised to the iptacopan arm and all patients randomised to the placebo arm who were then treated with iptacopan in the open-label period. ○ This analysis set was used to analyse iptacopan efficacy data and the analysis considered all data collected after the first administration of iptacopan. This excluded any patients without a randomisation number, those who were mis-randomised and patients who were randomised to placebo but not treated with iptacopan in the open-label period • Safety set (SAF): included all patients who received at least one dose of study treatment. Patients were analysed according to the study treatment they received • Combined safety set (CSAF): included all patients who received at least one dose of iptacopan during the double-blind treatment period or the open-label treatment period ○ The CSAF was used to analyse long-term iptacopan safety data, and the analysis considered all data collected after the first administration of iptacopan
Statistical analysis of primary endpoint(s)	Primary analysis of the 6-month double-blind period: <i>Hypothesis:</i> • That iptacopan is superior to placebo in reducing proteinuria at 6 months of treatment. • The null hypothesis that the mean of the log-transformed ratio to baseline of UPCR at Month 6 for the iptacopan group is greater than or equal to that of the placebo group ($H_0: \mu_{\text{iptacopan}} - \mu_{\text{placebo}} \geq 0$) was tested against a one-sided alternative hypothesis of the mean for the iptacopan group being less than that for the placebo group ($H_A: \mu_{\text{iptacopan}} - \mu_{\text{placebo}} < 0$) <i>Statistical testing</i> • The primary comparison between iptacopan and placebo was defined as a one-sided hypothesis, which was tested at the one-sided

APPEAR-C3G	Description
	0.025 level • The primary analyses were based on the FAS • At baseline and Month 6, the geometric mean of two 24h UPCR values obtained from two distinct 24h urine collections was used in the analysis as the 24h UPCR measurement for that visit. In case only one 24h UPCR value was available, that value was used as the 24h UPCR measurement for that visit in the analysis • 24h UPCR measurements collected after initiation or intensification of antiproteinuric therapies or KRT were imputed, to reflect a poor response and also to reflect that 24h UPCR levels would deteriorate (increase) had these treatments not been received • Statistical analysis was performed using a mixed model for repeated measures (MMRM) for the log ratio to baseline in UPCR measurements. This model included treatment, time point, CS and/or MPA at randomisation (yes versus no) as fixed effects, treatment*time point as interaction term and log (baseline UPCR) as covariate. The correlations between visits within patients were modelled using an unstructured covariance matrix. The Kenward-Roger adjustment for degrees of freedom was used • If there were intercurrent events occurring in the study, the analysis was carried out in the imputed datasets. Each imputed dataset was analysed using the MMRM and the results were combined using Rubin's rules • The ratio of geometric means (iptacopan versus placebo) was presented for the 6-month time point together with the two-sided 95% CI and one-sided p-value for the hypothesis test. The study was considered positive if the one-sided p-value for the hypothesis test was <0.025 <i>Handling of intercurrent events</i> • Initiation or intensification of antiproteinuric therapies after randomisation: Values after the intake of additional antiproteinuric therapies were set to missing and imputed using the "jump to reference" (J2R) approach¹³² for the iptacopan arm and the missing-at-random (MAR) assumption for the placebo arm (hypothetical strategy) • Initiation of KRT after randomisation: Values after initiation of KRT were imputed using the J2R approach¹³² for the iptacopan arm and the MAR assumption for the placebo arm (hypothetical strategy) • Treatment discontinuation for any reason (other than the antiproteinuric therapies or KRT): 24h UPCR measurements after discontinuation of study treatment were collected and used in the analysis (treatment policy strategy) <i>Handling of missing values not related to intercurrent events</i> • The MMRM model used for the primary analysis implicitly imputes missing data under a MAR assumption
Statistical analysis of secondary endpoint(s)	Secondary endpoint analyses of the 6-month double-blind period: Analyses were performed based on the FAS.

APPEAR-C3G	Description
	Full details on the statistical approaches to measuring CfB in UPCR, CfB in eGFR, CfB in glomerular C3 deposit scores, circulating biomarker levels, histology total activity score and FACIT-Fatigue total score, and the proportion of patients who achieved the composite renal endpoint are presented in Appendix J.1.3 <i>Multiple test procedure</i> The hypotheses associated with the secondary endpoints were to be tested only if the null hypothesis associated with the primary endpoint was rejected. A multiple test procedure was used for testing the hypotheses associated with four secondary endpoints. Given the ultra-rare nature of the disease, the multiple test procedures controlled the familywise error rate of the secondary endpoints at one-sided 0.05 <i>Handling of intercurrent events for secondary analyses</i> In general, the same strategy as described for the primary endpoint was employed for handling intercurrent events applicable to the secondary endpoints. For the composite renal endpoint, the initiation or intensification of antiproteinuric therapies or initiation of KRT were considered as treatment failures via the composite strategy <i>Handling of missing values not related to intercurrent events for secondary analyses</i> In general, missing data were handled in the same way as described for the primary analysis. For the composite renal endpoint, patients were considered as treatment failures (i.e. non-responder imputation) in case of study discontinuation due to AE or renal death
Sample size, power calculation	The sample size was calculated to sufficiently power for testing the superiority of iptacopan versus placebo on proteinuria reduction (the primary endpoint of log-transformed ratio to baseline in UPCR at 6 months) - Assuming a reduction in UPCR of 60% in the iptacopan group versus 20% in the placebo group (i.e. a relative reduction versus placebo in UPCR of 50%) and a SD of 0.69 (on the log-scale) based on an interim analysis of the Phase 2 study, a sample size of 34 patients per group (total 68 patients) provided at least 98% power at a 1-sided significance level of 0.025 - Assuming a reduction in UPCR of 50% in the iptacopan group versus 20% in the placebo group (i.e. a relative reduction versus placebo in UPCR of 37.5%), a sample size of 68 patients provided at least 80% power at the 1-sided 0.025 significance level

Abbreviations: C3G, complement 3 glomerulopathy; CFAS, combined full analysis set; CfB, change from baseline; CI, confidence interval; CS, corticosteroid; CSAF, combined safety analysis set; eGFR, estimated glomerular filtration rate; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS, full analysis set; J2R, jump to reference; KRT, kidney replacement therapy; MAR, missing-at-random; MMRM, Mixed Model for Repeated Measures; MPA, mycophenolic acid; RAS, randomised analysis set; SAF, safety set; SCR, screening set; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

Sources: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data);³³ Bomback et al. 2022⁴⁸.

2.4.3 Clinical effectiveness results

The APPEAR-C3G trial provides the primary clinical evidence base for iptacopan. During the 6-month double-blind period, patients received either treatment with iptacopan or placebo. Following the double-blind period, all patients randomised to the placebo arm crossed over to open-label iptacopan treatment. All patients were then treated with iptacopan for another 6-month period, up to Month 12 of the study. Following completion of APPEAR-C3G, patients were able to continue treatment with iptacopan as part of an open-label extension study, the details of which are presented separately in Section 2.5.2.^{33, 38}

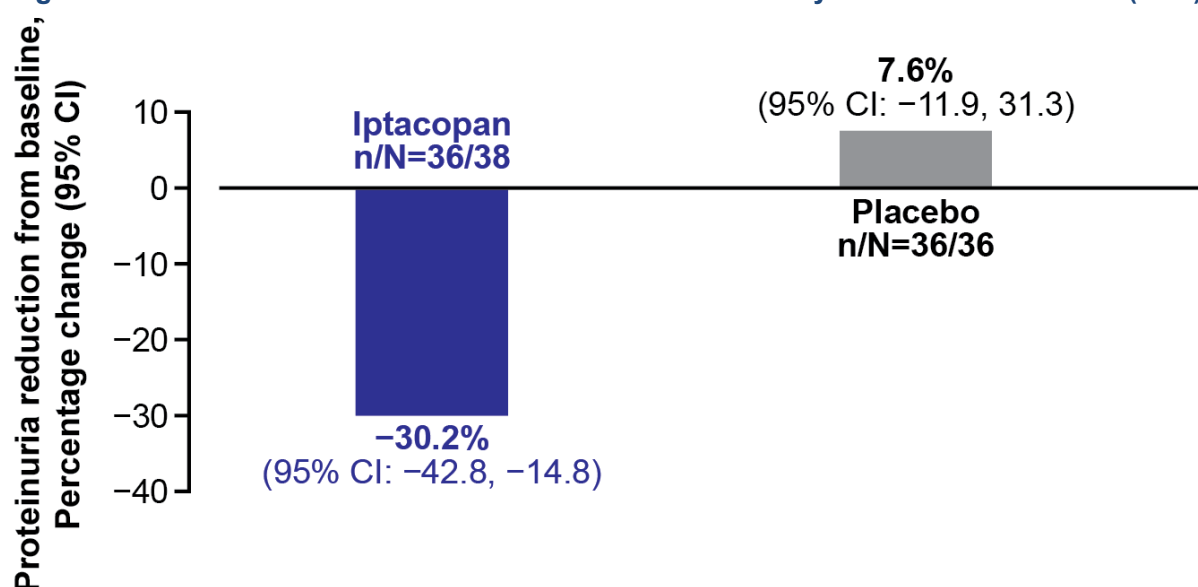
The following sections present the clinical efficacy data for iptacopan, as assessed in APPEAR-C3G.

2.4.3.1 Primary efficacy results: proteinuria reduction

Primary endpoint (double-blind period): CfB in 24h UPCR up to Month 6

APPEAR-C3G met its primary endpoint; iptacopan treatment resulted in a statistically significant and clinically meaningful relative reduction in 24h UPCR by 35.1% (95% CI: 13.8%, 51.1%; $p=0.0014$) following 6 months of treatment compared with placebo (both arms as add-on to background therapy) (Table 10). The adjusted mean ratios to baseline of 24h UPCR at the Day 180 visit using MMRM analysis in the iptacopan arm and the placebo arm were 0.70 (95% CI: 0.57, 0.85) and 1.08 (95% CI: 0.88, 1.31), respectively (i.e. reduction of 24h UPCR from baseline with iptacopan was 30% compared with an increase of 8% with placebo) (Figure 7; Table 10). These results demonstrate that treatment with iptacopan in patients with C3G reduces proteinuria compared with placebo.³³

Figure 7: Proteinuria reduction from baseline as measured by 24h UPCR at Month 6 (FAS)



Abbreviations: CI, confidence interval; ERA, European Renal Association; FAS, full analysis set; N, number of all patients included in the analysis (with non-missing baseline and covariates); n, number of patients with values non-missing and not imputed as per intercurrent event handling strategy at designated visit; UPCR, urine protein-to-creatinine ratio.

Sources: Kavanagh et al. Oral. Presented at ERA Congress 2024;¹²⁶ Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-1).³³

Table 10: MMRM analysis of log-transformed ratio to baseline in 24h UPCR (g/g) up to Month 6 (FAS)

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d, versus placebo		
					Geometric adjusted ratio (95% CI)	% Reduction (95% CI)	1-sided p-value
Day 90	Iptacopan	38	36	0.601 (0.493, 0.731)	0.603 (0.454, 0.800)	39.7 (20.0, 54.6)	-
	Placebo	36	35	0.996 (0.816, 1.217)			
Day 180	Iptacopan	38	36	0.698 (0.572, 0.852)	0.649 (0.489, 0.862)	35.1 (13.8, 51.1)	0.0014
	Placebo	36	36	1.076 (0.881, 1.313)			

Intercurrent events handled with hypothetical strategy: values after the initiation or intensification of antiproteinuric therapies and KRT were multiply imputed under J2R and MAR for the iptacopan and placebo groups, respectively. MMRM was used and included treatment, visit, CS or MPA treatment at randomisation (yes versus no) as fixed effects, treatment*visits as interaction term and log (baseline UPCR) as covariate. Correlations between visits within patients were modelled using an unstructured covariance matrix. Model was fit on log-transformed UPCR ratio.

Abbreviations: b.i.d., twice daily; CI, confidence interval; CS, corticosteroid; eGFR, estimated glomerular filtration rate; FAS, full analysis set; J2R, jump to reference; KRT, kidney replacement therapy; MAR, missing-at-random; MMRM, Mixed Model of Repeated Measures; MPA, mycophenolic acid; N, number of all patients included in the analysis (with non-missing baseline and covariates); UPCR, urine protein-to-creatinine ratio.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-1).³³

Primary endpoint (double-blind period): sensitivity analyses

Pre-specified sensitivity analyses for the primary endpoint considered alternative imputation approaches following intercurrent events. Intercurrent events were rare, reported in only three patients (7.9%) in the iptacopan arm. The sensitivity analyses, presented in Table 11, are consistent with the primary analysis, confirming robustness to varying assumptions on the handling of intercurrent events. This is expected given that only one intercurrent event (increasing CS dose) required imputation based on the hypothetical strategy. The other two intercurrent events were treatment discontinuations in the iptacopan arm; UPCR measurements after treatment discontinuation were used in the primary analysis as per the treatment policy strategy. Additional post-hoc sensitivity analyses were conducted due to observed imbalances at baseline to assess the impact of adjustment for these baseline covariates (Table 11).³³

Table 11: Summary of sensitivity analyses for primary endpoint at Month 6 (FAS)

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		% Reduction (95% CI)	1-sided p-value
Pre-specified sensitivity analyses			
Log-transformed ratio to baseline in UPCR (sampled from 24h urine)	Primary analysis: “Jump to reference” imputation approach following the intercurrent event ^a	35.1 (13.8, 51.1)	0.0014
	Sensitivity analysis 1: Imputation under the MAR assumption following the intercurrent event ^a	35.7 (14.7, 51.6)	0.0011

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Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		% Reduction (95% CI)	1-sided p-value
collection) at Month 6	Sensitivity analysis 2: “Copy-reference” imputation approach following the intercurrent event ^a	35.4 (14.3, 51.3)	0.0012
Post-hoc sensitivity analyses			
Log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at Month 6	Post-hoc sensitivity analysis 1: Adjustment for baseline eGFR (mL/min/1.73 m ²)	35.0 (13.4, 51.2)	0.0016
	Post-hoc sensitivity analysis 2: Adjustment for age group at C3G diagnosis ^b	35.8 (14.2, 52.0)	0.0014
	Post-hoc sensitivity analysis 3: Adjustment for C3G subtype at diagnosis ^c	38.4 (17.5, 54.1)	0.0006

^aHypothetical strategy was applied to handle intercurrent event of increasing corticosteroid dose (one event occurred at study Day 106 in the iptacopan group). Treatment policy strategy was applied to handle two intercurrent events of treatment discontinuation for all analyses. ^bAge group at C3G diagnosis was categorised as <18 years and ≥18 years. ^cC3G subtype at diagnosis was categorised as C3GN and other.

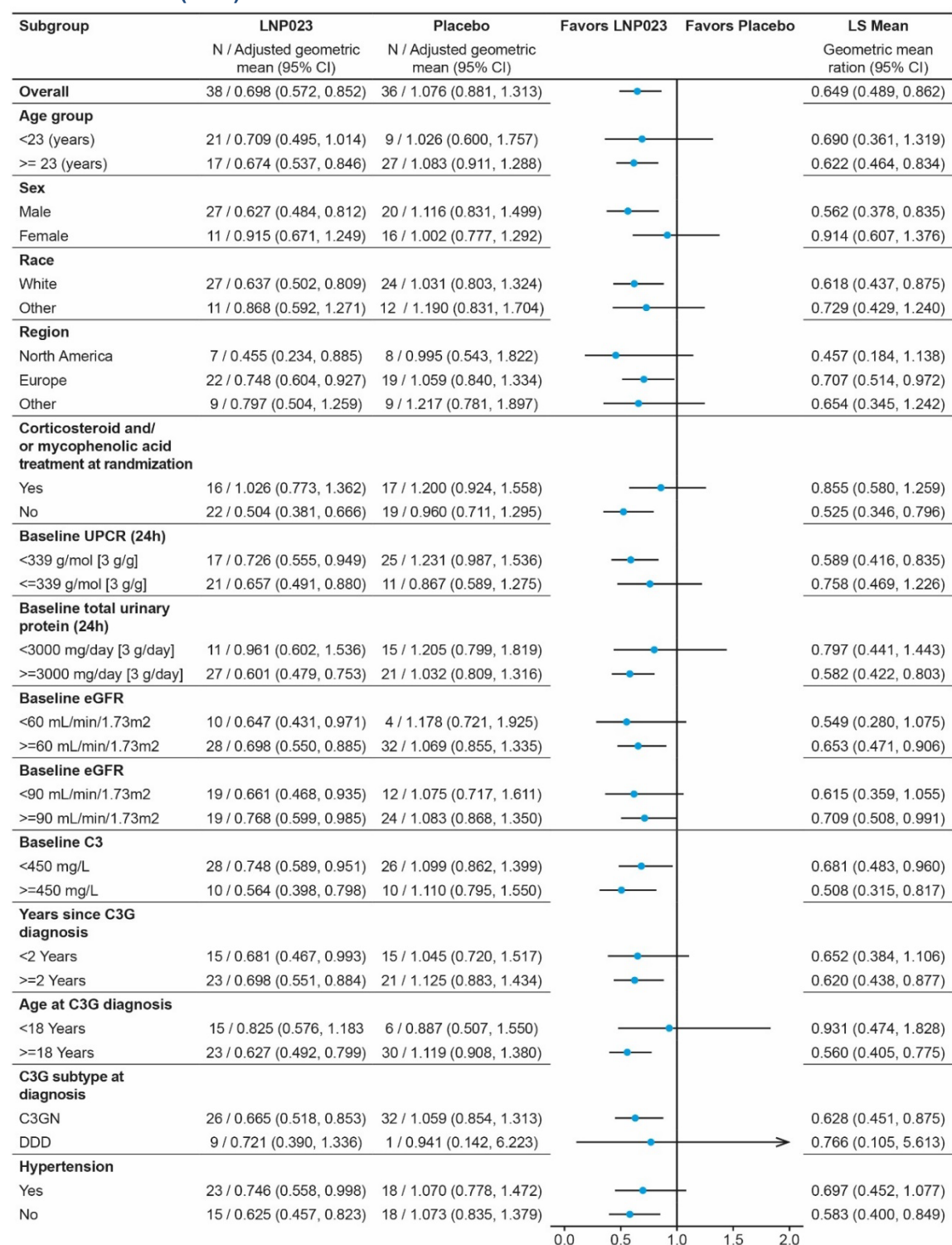
Abbreviations: b.i.d., twice daily; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; MAR, missing-at-random; UPCR, urine protein-to-creatinine ratio.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-3; Figure 11-4).³³

Primary endpoint (double-blind period): pre-specified subgroup analyses

Pre-specified subgroup analyses of the primary endpoint are presented in Figure 8. Iptacopan consistently improved 24h UPCR at Day 180 versus placebo across subgroups, including demographics (such as age, sex, race) and baseline disease characteristics (including UPCR, eGFR, and C3G subtype). However, due to the small sample size in the subgroups, the precision of the estimates is low, as indicated by wide confidence intervals for some subgroups.³³

Figure 8: Forest plot of subgroup analysis of log-transformed ratio to baseline in UPCR 24h at Month 6 (FAS)



Log transformed ratio to baseline was analysed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as an interaction term and log (baseline UPCR) as a covariate, unless the stratification variable was removed per SAP specified strategy.

Abbreviations: C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; MMRM, mixed model for repeated measures; SAP, statistical analysis plan; UPCR, urine protein-to-creatinine ratio.

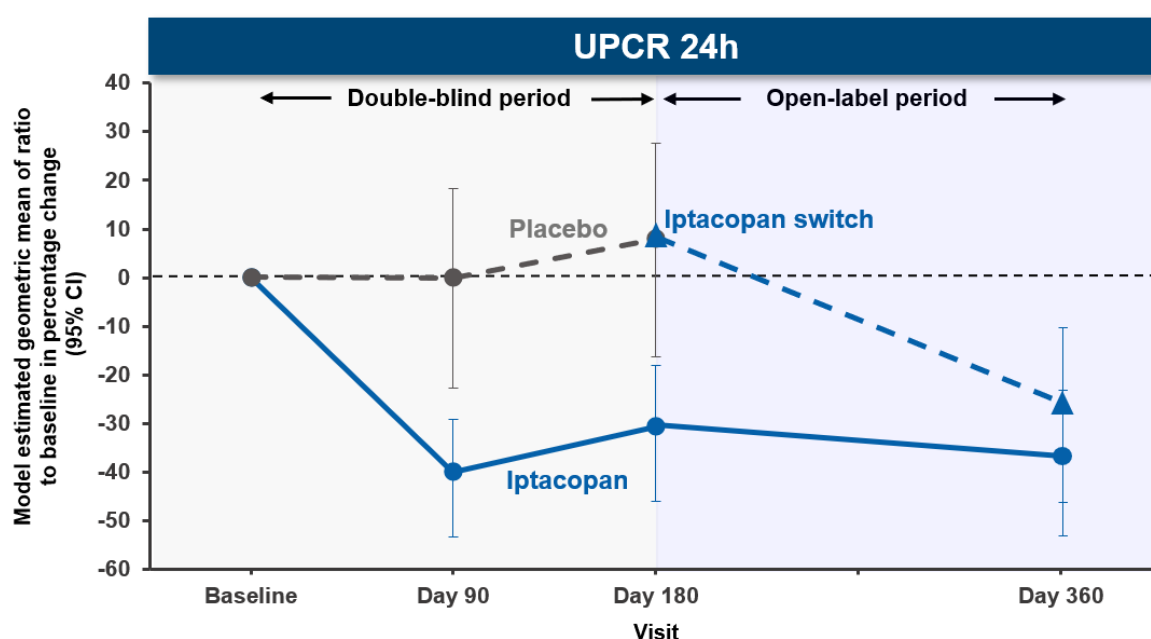
Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Figure 11–6)³³

Primary endpoint (open-label period): CfB in 24h UPCR up to Month 12

Results from the open-label period of APPEAR-C3G demonstrated that in patients initially randomised to iptacopan, the observed reduction in 24h UPCR was sustained up to Month 12 (40% geometric mean reduction from baseline; geometric mean ratio 0.60 [95% CI: 0.45, 0.80]; Table 12).³³

Patients initially randomised to the placebo arm who switched to open-label iptacopan at Month 6 had a 27% UPCR reduction from baseline to Month 12 (geometric mean ratio 0.73 [95% CI: 0.58, 0.92]; Table 12). Considering the rise in UPCR between baseline and Month 6 (while on placebo), the reduction in UPCR from Month 6 to Month 12 (on iptacopan) was 31%, which was similar to the reduction observed in the iptacopan arm from baseline to Month 6 (34%) (Table 12). The 24h UPCR reduction up to Month 12 is presented in Figure 9.³³

Figure 9: Geometric mean reduction in 24h UPCR from baseline up to Month 12 (FAS)



MMRM model including treatment, visit, CS or MPA treatment at randomisation (yes versus no) as fixed effects, treatment visits as interaction term and log (baseline UPCR) as covariates. Analysis uses all non-missing data including following an intercurrent event; no imputation of missing data. Placebo-iptacopan switch data based on unadjusted geometric mean.

Abbreviations: ASN, American Society of Nephrology; CI, confidence interval; CS, corticosteroid; FAS, full analysis set; MMRM, Mixed Model for Repeated Measures; MPA, mycophenolic acid; UPCR, urine protein-to-creatinine ratio.

Source: Nester et al. Oral. Presented at ASN Kidney Week 2024.¹³⁰

Table 12: Geometric mean ratio of CfB in 24h UPCR (g/g) up to Month 12 by treatment group (FAS)

Visits	Statistics	Iptacopan 200mg b.i.d. (N=38)	Placebo-iptacopan switch ^a (N=36)
Day 90	Geometric mean ^b	0.56	1.00
	95% CI	0.45–0.71	0.83–1.20
Day 180 ^a	Geometric mean	0.66	1.09
	95% CI	0.51–0.85	0.92–1.28
Day 360	Geometric mean	0.60	0.73

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Visits	Statistics	Iptacopan 200mg b.i.d. (N=38)	Placebo-iptacopan switch ^a (N=36)
	95% CI	0.45–0.80	0.58–0.92

^aThe switch from placebo to iptacopan 200 mg b.i.d. took place following the Day 180 visit. ^bGeometric mean was calculated by back transforming the mean of the log-transformed data.

Abbreviations: b.i.d., twice daily; CfB, change from baseline; CI, confidence interval; FAS, full analysis set; N, number of patients in the full analysis set; UPCR, urine protein-to-creatinine ratio.

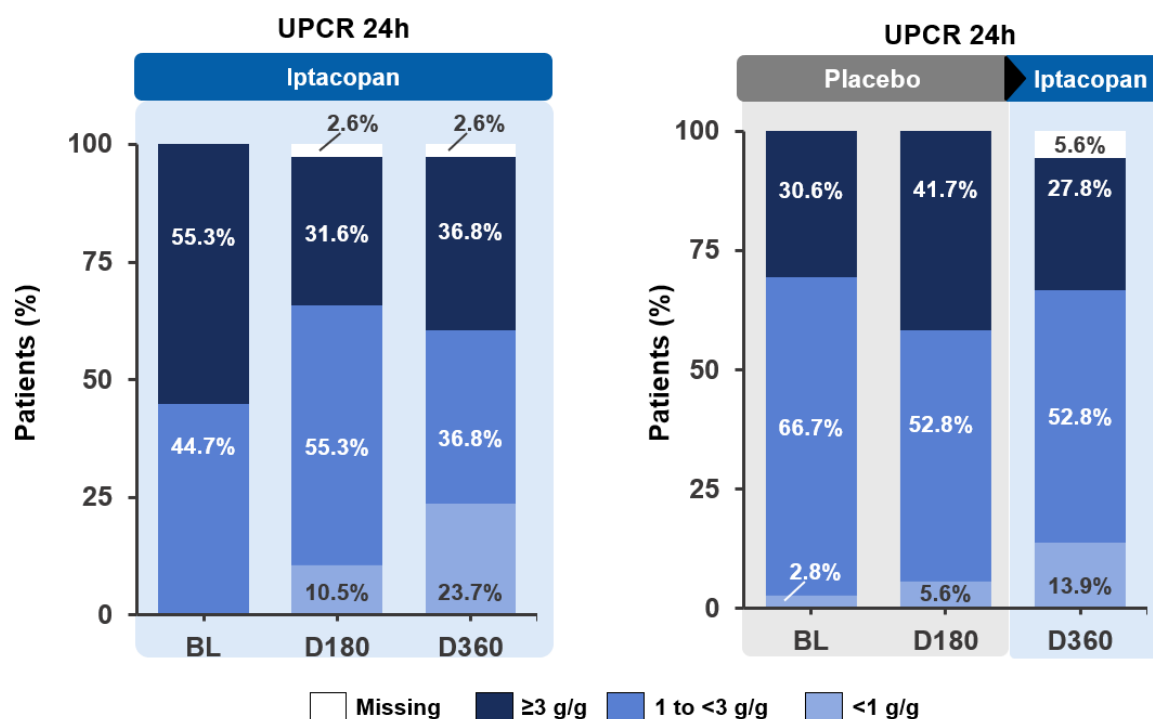
Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-4).³³

Supplementary analyses for primary efficacy results

A post-hoc analysis evaluated the proportion of patients with nephrotic-range proteinuria, defined as ≥ 3 g/g (339 g/mol) 24h UPCR. In the iptacopan arm, the proportion of participants with nephrotic range proteinuria decreased from 55.3% at baseline to 31.6% at Month 6 and 36.8% at Month 12 (Figure 10). In the placebo arm, during the double-blind period, the proportion of patients with nephrotic-range proteinuria increased from 30.6% at baseline to 41.7% at Month 6. Following switch to open-label iptacopan at Month 6, the proportion decreased to 27.8% at Month 12 (Figure 10).³³

Furthermore, in the iptacopan arm there was an increase in the proportion of patients achieving UPCR < 1 g/g (< 113 g/mol) at Month 12, from 0% at baseline to 10.5% at Month 6 and 23.7% at Month 12 (Figure 10). In the placebo arm, the proportion with UPCR < 1 g/g increased marginally from 2.8% at baseline to 5.6% at Month 6. After switch to iptacopan at Month 6, it increased to 13.9% at Month 12 (Figure 10).³³

Figure 10: Proportion of patients with different levels of 24h UPCR up to Month 12 (FAS)



Abbreviations: ASN, American Society of Nephrology; BL, baseline; D, Day; FAS, full analysis set; UPCR, urine protein-to-creatinine ratio.

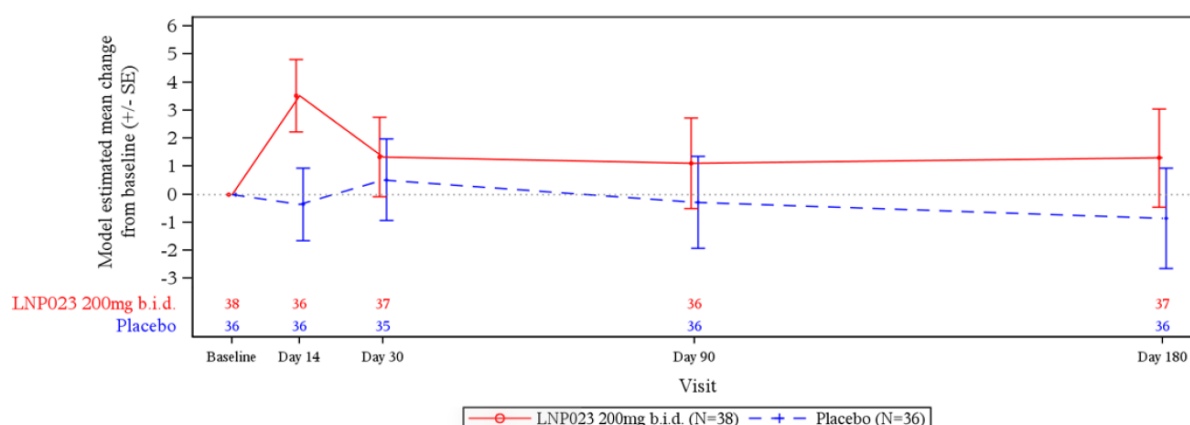
Source: Nester et al. Oral. Presented at ASN Kidney Week, 2024¹³⁰

2.4.3.2 Secondary efficacy results: eGFR

Secondary endpoint: CfB in eGFR up to Month 6

A numerical improvement in eGFR was observed in the iptacopan arm compared with the placebo arm at Month 6. At this time point the adjusted mean changes from baseline in eGFR (mL/min/1.73m²) in the iptacopan arm and the placebo arm were 1.30 (95% CI: -2.14, 4.73) and -0.86 (95% CI: -4.36, 2.64), respectively (Table 13). The adjusted mean difference of iptacopan versus placebo was 2.16 mL/min/1.73m² (95% CI: -2.75, 7.06; multiplicity-adjusted 1-sided p-value: 0.3241).³³ The mean change in eGFR from baseline to 6 months for the two study arms is presented in Figure 11.³³

Figure 11: Mean change of eGFR from baseline up to Month 6 (FAS)



CfB in eGFR was analysed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as interaction term and baseline eGFR as covariate. Correlations between visits within participants were modelled using an unstructured covariance matrix.

Abbreviations: b.i.d., twice daily; CfB, change from baseline; eGFR, estimated glomerular filtration rate; FAS, full analysis set; MMRM, Mixed Model for Repeated Measures; N, number of all patients included in the analysis (with non-missing baseline and covariates); SE, standard error.

Source: Kavanagh et al. Oral. Presented at ERA Congress, 2024.¹²⁶

Table 13: MMRM for CfB in eGFR (mL/min/1.73m²) at Month 6 (FAS)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	Nominal 1-sided p-value
Day 180	Iptacopan	38	37	1.295 (-2.136, 4.726)	2.156 (-2.749, 7.061)	0.1945
	Placebo	36	36	-0.861 (-4.357, 2.635)		

Intercurrent events handled with the following strategy: values after initiation or intensification of antiproteinuric therapies were multiply imputed under J2R and MAR for iptacopan and placebo groups, respectively. Treatment discontinuation for any reason was handled with treatment policy strategy. Change from baseline in eGFR was analysed using a MMRM which included treatment, visit, and stratification variable as fixed effects, treatment*visits as interaction term and baseline eGFR as covariate. Correlations between visits within patients were modelled using an unstructured covariance matrix.

Abbreviations: b.i.d., twice daily; CfB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; J2R, jump to reference; MAR, missing-at-random; MMRM, Mixed Model of Repeated Measures; N, number of all patients included in the analysis (with non-missing baseline and covariates); UPCR, urine protein-to-creatinine ratio.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-6).³³

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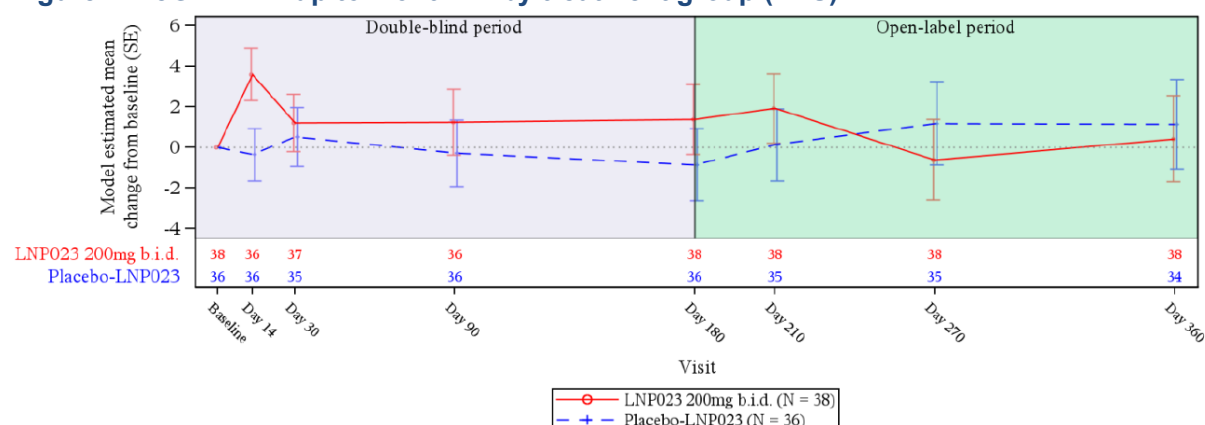
The pre-specified analysis of CfB in eGFR included the background immunosuppression stratification factor (CS and/or MPA treatment at randomisation) and baseline eGFR as covariates. Given the observed imbalances at baseline for several baseline characteristics, additional post-hoc sensitivity analyses were carried out to assess the impact of adjustment for other baseline covariates. The adjustments for age at C3G diagnosis or subtype of C3G yielded results consistent with the pre-specified analysis.³³

However, when the analysis was adjusted for baseline UPCR, the adjusted mean CfB in eGFR (mL/min/1.73m²) was 1.76 (95% CI: -1.59, 5.11) for iptacopan versus -1.44 (95% CI: -4.86, 1.98) for placebo. This results in an adjusted mean difference of 3.20 mL/min/1.73m² for iptacopan compared to placebo (95% CI: -1.61, 8.01; 1-sided p=0.0963).³³

Exploratory endpoint: CfB in eGFR up to Month 12

Results from the open-label period of APPEAR-C3G demonstrated that the change in eGFR from baseline to Month 12 was sustained in the iptacopan arm. Iptacopan treatment also numerically increased eGFR in the placebo-iptacopan switch arm after switching to iptacopan at the start of the open-label period (Figure 12). The mean changes from baseline in eGFR in the iptacopan arm and the placebo-iptacopan switch arm were 0.44 mL/min/1.73m² (95% CI: -3.76, 4.64) and 1.15 mL/min/1.73m² (95% CI: -3.22, 5.53), respectively at Day 360 (Table 14). Patients in the placebo-iptacopan switch arm had a mean change in eGFR of 2.54 mL/min/1.73m² during the open-label period.³³

Figure 12: eGFR CfB up to Month 12 by treatment group (FAS)



CfB in eGFR was analysed using a MMRM which included treatment, visit, stratification, variable as fixed effect, treatment*visit as an interaction term and baseline eGFR as a covariate. Correlations between visits within participants were modelled using an unstructured covariance matrix. Vertical bars represent SE. **Abbreviations:** b.i.d., twice daily; CfB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; N, number of participants in full analysis set; SE, standard error. **Source:** Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Figure 11–12).³³

Table 14: MMRM analysis of CfB in eGFR (mL/min/1.73m²) up to Month 12 (FAS)

Visit	Treatment	N	n	Iptacopan 200 mg b.i.d. versus Placebo	
				Adjusted mean [SE] (95% CI)	Adjusted mean difference (95% CI)
Day 180	Iptacopan	38	38	1.382 [1.723] (-2.052, 4.817)	2.230 (-2.700, 7.160)
	Placebo	36	36	-0.848 [1.770] (-4.375, 2.680)	-
	Iptacopan	38	38	0.439 [2.106] (-3.762, 4.641)	-

Visit	Treatment	N	n	Iptacopan 200 mg b.i.d. versus Placebo	
				Adjusted mean [SE] (95% CI)	Adjusted mean difference (95% CI)
Day 360	Placebo-iptacopan switch	36	34	1.152 [2.194] (-3.222, 5.526)	-

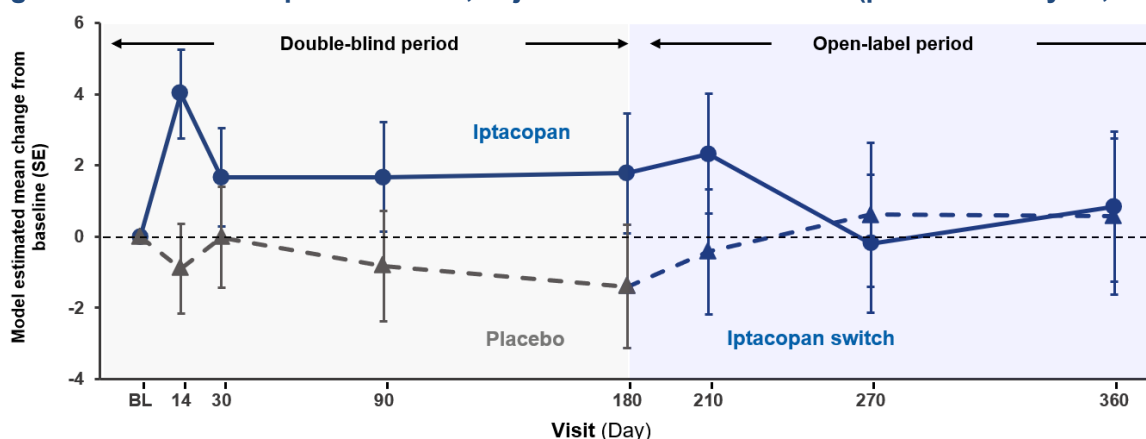
Following Day 180, patient randomised to the placebo arm were receiving treatment with iptacopan in the open-label period. Intercurrent events handled with the following strategy: values after the initiation or intensification of antiproteinuric therapies, initiation of KRT, and treatment discontinuation for any reason were handled with a treatment policy strategy. CfB in eGFR was analysed using all observed data via an MMRM which included treatment, visit, and stratification variable as fixed effects, treatment*visit as an interaction term, and baseline eGFR as a covariate. Correlations between visits within patients were modelled using an unstructured covariance matrix.

Abbreviations: b.i.d., twice daily; CfB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; I/C, intercurrent events; KRT, kidney replacement therapy; MMRM, Mixed Model of Repeated Measures; N, number of all patients included in the analysis (with non-missing baseline and covariates); n, number of patients with values non-missing and not imputed as per I/C handling strategy at designated visit; SE, standard error.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-7).³³

Due to the observed imbalance in baseline UPCR between the iptacopan and placebo arms, an additional post-hoc analysis was carried out to assess the impact of adjusting for baseline UPCR as a covariate. The adjusted mean changes from baseline in eGFR in the iptacopan arm and the placebo-iptacopan switch arm were 0.84 mL/min/1.73m² (95% CI: -3.36, 5.05) and 0.57 mL/min/1.73m² (95% CI: -3.81, 4.96), respectively at Day 360 (see Figure 13 and Table 15).³³

Figure 13: eGFR CfB up to Month 12, adjusted for baseline UPCR (post hoc analysis; FAS)



MMRM model including treatment, visit, corticosteroid or mycophenolic acid treatment at randomisation (yes versus no) as fixed effects, treatment visits as interaction term and baseline eGFR and log (baseline UPCR) as covariates. Analysis uses all non-missing data including following an intercurrent event; no imputation of missing data. **Abbreviations:** CfB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; MMRM, Mixed Model of Repeated Measures; SE, standard error; UPCR, urine protein-to-creatinine ratio.

Sources: Nester et al. Oral. Presented at ASN Kidney Week, 2024;¹³⁰ Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Figure 11-13).³³

Table 15: MMRM analysis of CfB in eGFR (mL/min/1.73m²) up to Month 12, adjusted for baseline UPCR (post hoc analysis; FAS)

Visit	Treatment	N	n	Iptacopan 200 mg b.i.d. versus Placebo	
				Adjusted mean [SE] (95% CI)	Adjusted mean difference (95% CI)
Day 180	Iptacopan	38	38	1.787 [1.683] (-1.568, 5.141)	3.185 (-1.657, 8.028)
	Placebo	36	36	-1.399 [1.733] (-4.852, 2.055)	-
	Iptacopan	38	38	0.844 [2.107] (-3.360, 5.048)	-

Visit	Treatment	N	n	Iptacopan 200 mg b.i.d. versus Placebo	
				Adjusted mean [SE] (95% CI)	Adjusted mean difference (95% CI)
Day 360	Placebo-iptacopan switch	36	34	0.572 [2.199] (−3.814, 4.957)	-

CfB in eGFR was analysed using all observed data via a MMRM which included treatment, visit, and stratification variable as fixed effects, treatment*visit as an interaction term, baseline eGFR and log-transformed baseline UPCR 24 hours as covariates.

Correlations between visits within participants were modelled using an unstructured covariance matrix. I/Cs handled with the following strategy: values after the initiation or intensification of antiproteinuric therapies, initiation of KRT, and treatment discontinuation for any reason were handled with a treatment policy strategy.

Abbreviations: CfB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; I/C, intercurrent event; KRT, kidney replacement therapy; MMRM, Mixed Model of Repeated Measures; N, number of all participants included in the analysis (with non-missing baseline and covariates); n, number of participants with values non-missing and non-missing baseline at the designated visit; SE, standard error; UPCR, urine protein-to-creatinine ratio.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 14.2–3.6.2).³³

Exploratory endpoint: eGFR slope change analyses

In addition to the CfB analyses, eGFR data were also analysed to assess the change in annualised eGFR slope with iptacopan treatment compared to patients' eGFR trajectory prior to iptacopan initiation.

For this purpose, historical serum creatinine data were collected for the patients enrolling in APPEAR-C3G. Study sites were instructed to provide all available serum creatinine values from the 2 years prior to the screening visit. All data within that period were accepted provided there was a corresponding date of sample collection. Historical eGFR values were derived from serum creatinine measurements using the CKD-EPI formula, consistent with the eGFR calculations for measurements collected during the APPEAR-C3G study.³³

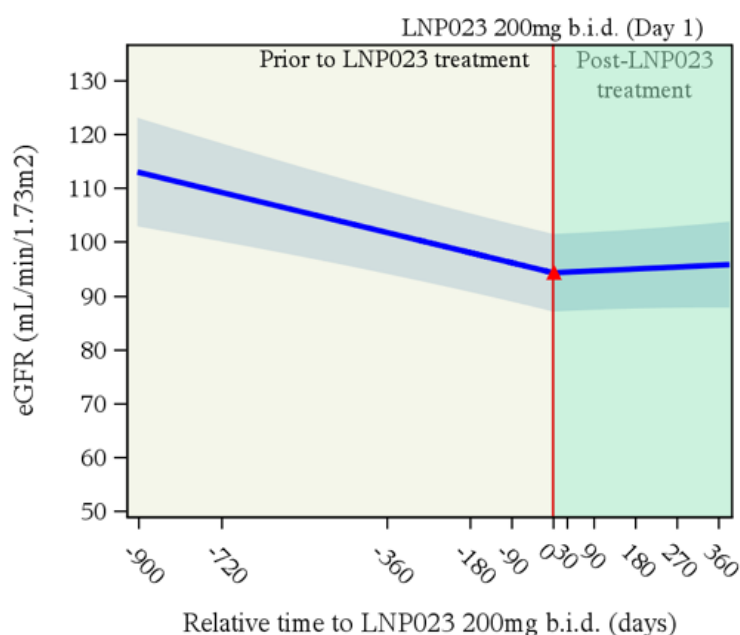
For the eGFR slope change analyses, the historical data were combined with all observed in-study eGFR data. Pre-iptacopan eGFR data were defined as measurements before initiation of iptacopan treatment and thus included the historical values (up to 2 years or since C3G diagnosis if less than 2 years) as well as screening/run-in data and placebo arm data from the 6-month double-blind period of APPEAR-C3G. This resulted in participants randomised to placebo contributing up to 2.5 years of eGFR data to the pre-iptacopan slope, while participants randomised to iptacopan contributed up to 2 years of data to the pre-iptacopan slope. Overall, the pre-iptacopan slope was derived from 494 eGFR observations in 74 patients, comprising of 198 historical observations, 146 during the screening/run-in period, and 150 from patients while receiving placebo in the double-blind period.³³

The on-iptacopan eGFR slope included data from the double-blind and open-label periods (Day 1 to 360) for patients randomised to the iptacopan arm and data from the open-label period (Day 180 to 360) for patients randomised to the placebo arm, after the patients had switched to iptacopan.³³

A longitudinal mixed effects model, with a common intercept, a pre-iptacopan slope and a change in the slope following iptacopan treatment was used to model the change in eGFR trajectory. Subject-level intercept and slope were included in the model as random effects. Missing data were handled implicitly through the model. The eGFR slope prior to iptacopan treatment and the change in slope after iptacopan treatment were estimated.³³

The mean pre-iptacopan eGFR slope was $-7.57 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $-10.57, -4.56$) in the full study population. Initiation of iptacopan led to stabilisation of eGFR, with eGFR slope for iptacopan estimated as $1.44 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $-2.18, 5.06$), which equated to a change in eGFR slope of $9.01 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $5.43, 12.60$; $p < 0.0001$) compared to the pre-iptacopan eGFR decline (Figure 14).³³ A longer-term eGFR slope analysis in the APPEAR-C3G population, including data from the open-label extension study, is presented in Section 2.5.2 and utilised in the economic model (Section 3.3.2).³³

Figure 14: eGFR slope change with iptacopan treatment – APPEAR-C3G (n=74) (FAS)



Number of patients: 74. The x-axis represents the relative study day to iptacopan (LNP023) treatment. Thick blue line shows the predicted eGFR over time; the shaded band is a pointwise 95% confidence interval. eGFR slopes per year were analysed using a linear mixed effects model including time (analysis day before or after change point [Day 1 of iptacopan treatment]) as a continuous covariate, patient-level intercept and slope (time) as random effects.

Abbreviations: b.i.d., twice daily; eGFR, estimated glomerular filtration rate; FAS, full analysis set.

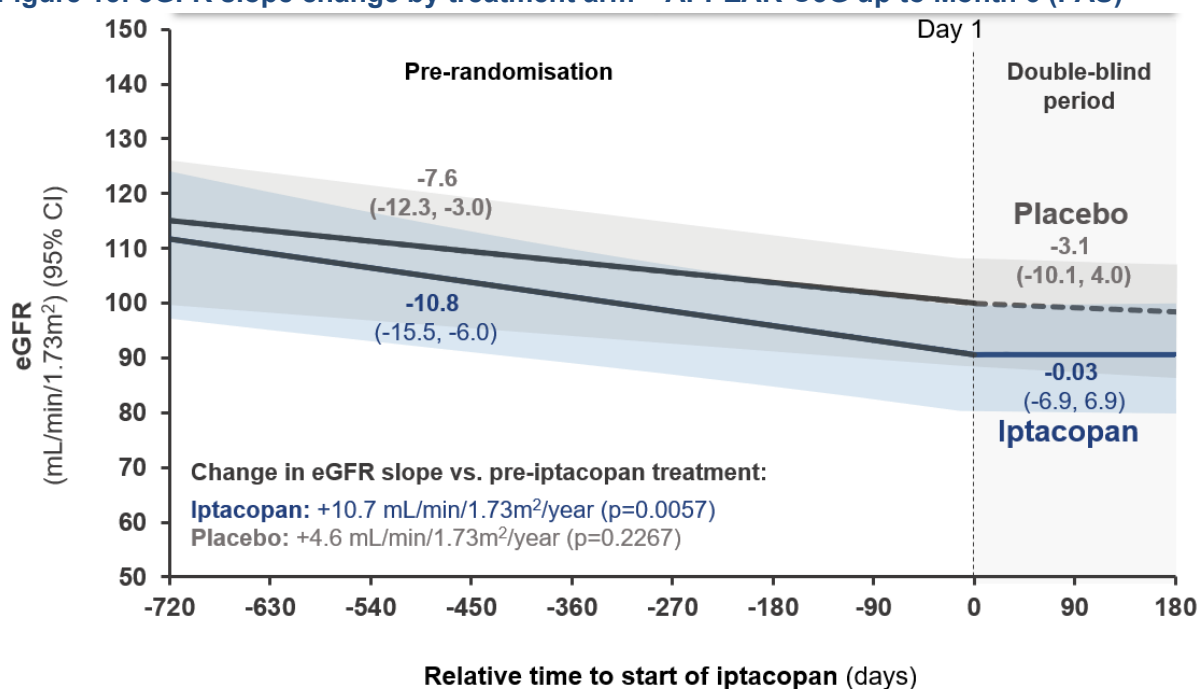
Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Figure 11-15, left panel).³³

In addition to the above pre-specified slope analysis, due to observed imbalances in some baseline characteristics between the iptacopan and placebo arms, an additional post-hoc analysis was conducted to compare annualised eGFR slope changes by treatment arm. In this analysis, the pre-randomisation eGFR slopes included data from the historical and screening/run-in periods only, analysed separately by arm, while eGFR slopes for the double-blind period were generated from iptacopan-arm and placebo-arm eGFR values following randomisation.³³

Annualised eGFR slopes are shown in Figure 15. Patients allocated to the iptacopan arm had a steeper mean eGFR decline pre-randomisation ($-10.75 \text{ mL/min/1.73 m}^2/\text{year}$) than patients allocated to the placebo arm ($-7.64 \text{ mL/min/1.73 m}^2/\text{year}$), consistent with baseline characteristics suggesting a more severe disease phenotype in the iptacopan arm than in the placebo arm (Table 7). Following start of iptacopan treatment, the available data suggest a stabilisation in the iptacopan arm eGFR slope ($-0.03 \text{ mL/min/1.73 m}^2/\text{year}$; 95% CI: $-6.93, 6.88$). In the placebo arm, eGFR continued to decline, however, at a lower rate than prior to trial inclusion ($-3.08 \text{ mL/min/1.73 m}^2/\text{year}$; 95% CI: $-10.13, 3.97$). Slope change per year for the iptacopan arm and placebo arm, respectively, is presented in Table 16; while the change in slope Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

was nominally significant in the iptacopan arm ($p=0.0057$), it was not in the placebo arm ($p=0.2267$).³³

Figure 15: eGFR slope change by treatment arm – APPEAR-C3G up to Month 6 (FAS)



Number of patients: iptacopan $n=38$; placebo $n=36$. eGFR slopes per year were analysed using a linear mixed effects model including time (analysis day before or after change point [Day 1 of iptacopan treatment]) as a continuous covariate, participant-level intercept and slope (time) as random effects. Intercurrent events handled with a treatment policy strategy.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set.

Source: Nester et al. Oral. Presented at ASN Kidney Week, 2024.¹³⁰

Table 16: Annualised eGFR slope change analysis (FAS)

Treatment	Slope of pre-randomisation period per year (95% CI)	Slope of double-blind period per year (95% CI)	Slope change per year (95% CI)	p-value
Iptacopan (N=38)	-10.753 (-15.510, -5.996)	-0.025 (-6.929, 6.878)	10.782 (3.230, 18.225)	0.0057
Placebo (N=36)	-7.641 (-12.279, -3.003)	-3.079 (-10.131, 3.973)	4.562 (-2.897, 12.021)	0.2267
Difference	-3.112 (-9.756, 3.531)	3.053 (-6.815, 12.922)	6.166 (-4.410, 16.742)	0.2490

eGFR slopes per year were analysed using a linear mixed effects model including treatment as a factor, time (analysis day before or day after study Day 1) as a continuous covariate, treatment*time as a fixed effect, participant-level intercept and slope (time) as random effects. Intercurrent events handled with a treatment policy strategy.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; N, number of all patients included in the analysis.

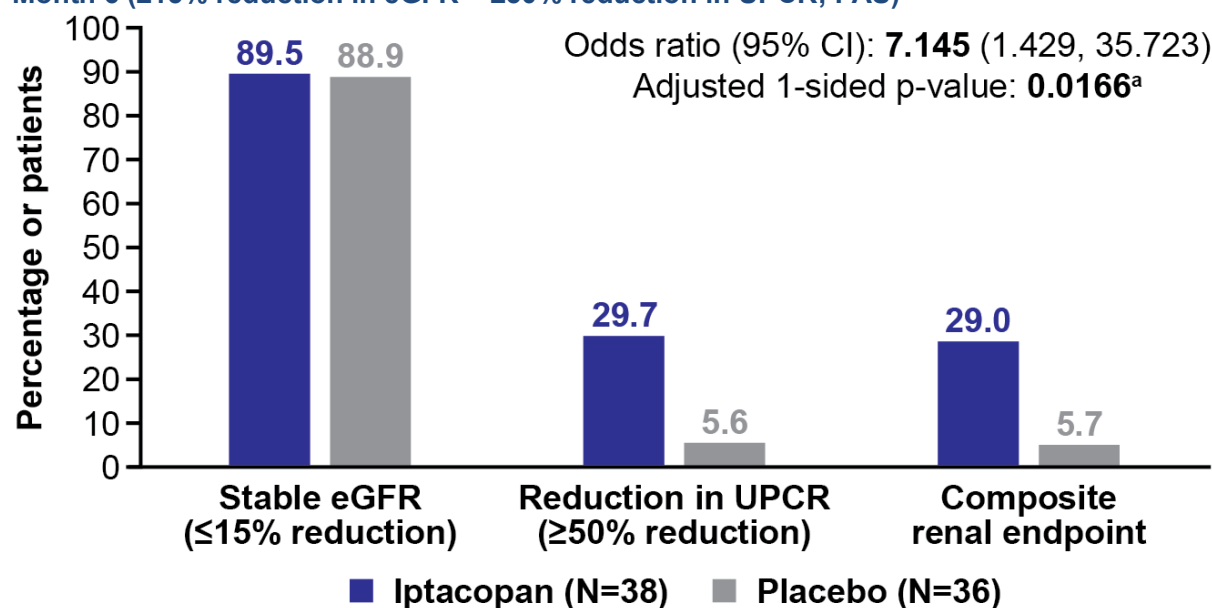
Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data Table 14.2–16.2.1).³³

2.4.3.3 Secondary efficacy results: composite renal endpoint

Secondary endpoint: composite renal endpoint at Month 6

Results from APPEAR-C3G demonstrated a statistically significant improvement in the proportion of participants achieving the composite endpoint of stable eGFR ($\leq 15\%$ decrease) and $\geq 50\%$ reduction in UPCR at Month 6 in patients treated with iptacopan versus placebo (multiplicity adjusted 1-sided $p=0.0166$). The marginal proportion of participants (95% CI) who achieved the composite renal endpoint at Month 6 was 29.0% (14.9%, 43.1%) in the iptacopan arm and 5.7% (-1.9%, 13.4%) in the placebo arm (Figure 16).³³

Figure 16: Marginal proportion of patients who achieved composite renal endpoint at Month 6 ($\leq 15\%$ reduction in eGFR + $\geq 50\%$ reduction in UPCR; FAS)



^aStatistically significant after adjustment for multiple testing.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; N, number of all patients included in the analysis (with non-missing baseline and covariates; UPCR, urine protein-to-creatinine ratio).

Source: Kavanagh et al. Oral. Presented at ERA Congress 2024.¹²⁶

Secondary endpoint: composite renal endpoint up to Month 12

The marginal proportion (95% CI) of participants who achieved the composite renal endpoint at Day 360 was 44.1% (28.9%, 59.4%) in participants randomised to the iptacopan arm, and 24.0% (9.9%, 38.1%) in participants randomised to the placebo arm who had switched to iptacopan at the start of the open-label period. This was similar to the proportion of patients who achieved the composite renal endpoint in the iptacopan arm during the double-blind period. Full results of the composite endpoint are presented in Table 17.³³

Table 17: Logistic regression of proportion of patients who achieved composite renal endpoint up to Month 12 (FAS)

Visit	Treatment	N	Stable eGFR (≤15% reduction) n/M (%)	Reduction in proteinuria (≥50% reduction) n/M (%)	Composite renal endpoint n/M ^a (%)	Marginal proportion (95% CI)	Difference in marginal proportions (95% CI) iptacopan versus placebo	OR (95% CI)
Day 180	Iptacopan	38	34/38 (89.5)	11/37 (29.7)	11/37 (29.7)	0.290 (0.149, 0.431)	0.233 (0.072, 0.394)	7.145 (1.429, 35.723)
	Placebo	36	32/36 (88.9)	2/36 (5.6)	2/36 (5.6)	0.057 (-0.019, 0.134) ^b	-	-
Day 360	Iptacopan	38	32/38 (84.2)	17/37 (45.9)	17/38 (44.7)	0.441 (0.289, 0.594)	-	-
	Placebo- iptacopan switch	36	30/34 (88.2)	10/34 (29.4)	8/34 (23.5)	0.240 (0.099, 0.381)	-	-

Intercurrent events handled in the following way: the initiation or intensification of antiproteinuric therapies or KRT was considered as treatment failures (or 0) via a composite strategy. Treatment discontinuation for any reason was handled with a treatment policy strategy. Odds ratio was obtained from a logistic regression model considering treatment and corticosteroid or mycophenolic acid treatment at randomisation (yes versus no) as factors: ^aConsidering the initiation or intensification of antiproteinuric therapies or KRT as treatment failures. ^bThe lower bound of the confidence interval is negative due to a low proportion of placebo patients achieved the composite renal endpoint.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; KRT, kidney replacement therapy; M, number of patients with non-missing response variable at designated visit; N, number of all patients in the full analysis set; n, number of patients who reached the endpoint at designated visit; OR, odds ratio.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-10; Table 14-2–4-4).³³

2.4.3.4 Secondary efficacy results: C3G histologic total activity score

Secondary endpoint: CfB in C3G histologic total activity score at Month 6

No significant differences were observed in the histologic total activity score from kidney biopsies after 6 months of iptacopan treatment in comparison with placebo. Treatment with iptacopan decreased the C3G histologic total activity score by an adjusted mean of -1.95 (95% CI: -2.69 , -1.20); in the placebo arm, an adjusted mean decrease of -1.11 (95% CI: -1.83 , -0.39) was observed, resulting in a non-statistically significant difference (Table 18).³³

Table 18: CfB in histologic total activity score at Month 6 (FAS)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	1-sided p-value
Day 180	Iptacopan	37	32	-1.946 (-2.691 , -1.201)	-0.833 (-1.872 , 0.205)	0.0579
	Placebo	36	34	-1.113 (1.831 , -0.394)	-	-

Intercurrent events handled with hypothetical strategy: values after the initiation or intensification of antiproteinuric therapies were multiply imputed using control-based pattern imputation for the iptacopan and placebo groups. Treatment discontinuation for any reason was handled with a treatment policy strategy. CfB in the histology total activity score was analysed using an ANCOVA model which included treatment, stratification variable as fixed effects and the baseline total activity score as covariate.

Abbreviations: ANCOVA, analysis of covariance; b.i.d., twice daily; CfB, change from baseline; CI, confidence interval; FAS, full analysis set; I/C, intercurrent event; n, number of participants with values non-missing and not imputed as per the I/C handling strategy at designated visit; N, number of all patients included in the analysis (with non-missing baseline and covariates).

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data Table 11-11).³³

Secondary endpoint: CfB in C3G histologic total activity score at Month 12

Only two patients from the iptacopan arm and four patients from the placebo-iptacopan switch arm had evaluable kidney biopsies at the end of the open-label period, as kidney biopsies were not mandatory at Month 12. In the two patients randomised to the iptacopan arm, the mean change in histologic total activity score from baseline to Month 12 was -2.0 (SD: 2.83). In the four patients randomised to the placebo-iptacopan switch arm, the mean change in histologic total activity score from Month 6 to Month 12 (during open-label treatment with iptacopan) was -1.5 (SD: 1.9).³³

2.4.3.5 Secondary efficacy results: FACIT-Fatigue total score

Secondary endpoint: CfB in FACIT-Fatigue at Month 6

Mean (SD) FACIT-Fatigue scores at baseline were near the general population norm for both treatment arms: 42.4 (10.08) in the iptacopan arm and 41.9 (8.91) in the placebo arm.

Participants taking iptacopan did not show an improvement in FACIT-Fatigue. The adjusted mean difference of CfB in the FACIT-Fatigue total score in the iptacopan arm versus placebo arm was -2.60 (95% CI: -6.03 , 0.84 ; multiplicity-adjusted 1-sided p-value: 0.9310) after 6 months of treatment (Table 19).³³

Table 19: MMRM analysis of CfB in FACIT-Fatigue total score at Month 6 (FAS)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	1-sided p-value
Day 180	Iptacopan	36	35	-0.410 (-2.755, 1.935)	-2.598 (-6.032, 0.835)	0.9310
	Placebo	31	31	2.188 (-0.334, 4.711)	-	-

I/Cs handled with the following strategy: values after initiation or intensification of antiproteinuric therapies were multiply imputed under J2R and MAR for iptacopan and placebo groups, respectively. Treatment discontinuation for any reason was handled with treatment policy strategy. Change from baseline in the FACIT-Fatigue total score was analysed using MMRM which included treatment, visit, corticosteroid or mycophenolic acid treatment at randomization (yes versus no) as fixed effects, treatment*visit as interaction term and the baseline FACIT-Fatigue total score as covariate. Correlations between visits within participants were modelled using an unstructured covariance matrix.

Abbreviations: b.i.d., twice daily; CfB, change from baseline; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set; I/C, intercurrent event; J2R, jump to reference; MAR, missing at random; MMRM, Mixed Model of Repeated Measures; n, number of participants with values non-missing and not imputed as per the I/C handling strategy at designated visit; N, number of all patients included in the analysis (with non-missing baseline and covariates).

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data Table 11-13).³³

Secondary endpoint: CfB in FACIT-Fatigue at Month 12

At Month 12, the adjusted mean changes from baseline in the FACIT-Fatigue total score in the iptacopan and placebo-iptacopan switch arms were -0.78 (95% CI: -3.18, 1.63) and 2.72 (95% CI: 0.07, 5.37), respectively.³³

2.4.3.6 Exploratory efficacy results: glomerular C3 deposit scores

Exploratory endpoint: CfB in glomerular C3 deposit scores at Month 6

Treatment with iptacopan reduced glomerular C3 deposition in kidney biopsies, as measured by the adjusted mean difference in C3 deposit score between iptacopan versus placebo at Month 6 (-1.88 [95% CI: -3.30, -0.45]; 1-sided p=0.0053). Full results are presented in Table 20.³³

Table 20: CfB in glomerular C3 deposit scores at Month 6 (FAS)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	1-sided p-value
Day 180	Iptacopan	35	32	-0.781 (-1.811, 0.250)	-1.875 (-3.298, -0.452)	0.0053
	Placebo	36	35	1.094 (0.111, 2.078)	-	-

I/Cs handled with a treatment policy strategy: values after the initiation or intensification of antiproteinuric therapies and initiation of KRT were handled with a treatment policy strategy. Treatment discontinuation for any reason was also handled with a treatment policy strategy. CfB in C3 deposit score was analysed using an ANCOVA model which included treatment and stratification variable as fixed effects and baseline C3 deposit score as a covariate.

Abbreviations: ANCOVA, analysis of covariance; b.i.d., twice daily; C3, complement component 3; CfB, change from baseline; CI, confidence interval; FAS, full analysis set; I/C, intercurrent event; KRT, kidney replacement therapy; n, number of participants with values non-missing at designated visit; N, number of all patients included in the analysis (with non-missing baseline and covariates).

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data Table 11-14).³³

2.4.3.7 Exploratory efficacy results: effect of iptacopan on complement biomarkers

Exploratory endpoint: circulating biomarker levels at Month 6 and Month 12

Inhibition of the complement alternative pathway by iptacopan at Month 6 and Month 12 was validated via circulating biomarker levels, including serum C3, alternative pathway activity, plasma Bb, plasma sC5b-9 and urinary sC5b-9/creatinine. In patients with C3G, altered levels of complement biomarkers are indicative of alternative pathway dysregulation. This can include:

- Decreased serum C3
- Overactivity of alternative pathway activity, observed via Wieslab assay
- Increased plasma Bb
- Increased plasma sC5b-9
- Increased urinary sC5b-9 creatinine

With iptacopan treatment, there was a rapid rise in serum C3 levels, which was sustained throughout the study, while the C3 concentration in the placebo arm remained unchanged. In addition, decreases were observed with iptacopan in alternative pathway activity, plasma Bb, plasma sC5b-9 and urinary sC5b-9 (Table 21). Circulating biomarker levels were measured up to Month 12, to demonstrate the change in inhibition of the complement pathway following initiation of iptacopan treatment in the placebo-iptacopan switch arm. A sustained increase of serum C3 in the iptacopan arm was observed for the entire 12 months treatment period, as well as a rapid rise in placebo arm patients after switching to iptacopan at Day 180, mirroring the effect seen in the iptacopan arm in the double-blind period.³³

Table 21: Circulating biomarker levels up to Month 12 (FAS)

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus placebo
					% change (95% CI)
Serum C3					
Day 180	Iptacopan	38	38	2.853 (2.383, 3.416)	177.1 (114.1, 258.6)
	Placebo	36	36	1.030 (0.856, 1.238)	
Day 360	Iptacopan	38	38	3.107 (2.724, 3.543)	N/A
	Placebo-iptacopan switch	36	34	3.003 (2.622, 3.440)	
Alternative pathway activity (serum Wieslab assay [%]) ^a					
Day 180	Iptacopan	31	31	0.627 (0.516, 0.760)	-40.1 (-54.0, 21.8)
	Placebo	35	35	1.045 (0.871, 1.254)	
Day 360	Iptacopan	31	31	0.573 (0.539, 0.609)	N/A
	Placebo-iptacopan switch	35	33	0.604 (0.570, 0.640)	
Plasma Bb (ng/mL)					

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus placebo
					% change (95% CI)
Day 180	Iptacopan	31	31	0.951 (0.865,1.046)	-3.9 (-15.9, 9.9)
	Placebo	35	35	0.989 (0.905,1.082)	
Day 360	Iptacopan	31	31	1.062 (0.935,1.206)	N/A
	Placebo-iptacopan switch	35	35	1.126 (0.998,1.272)	
Plasma sC5b-9 (ng/mL)					
Day 180	Iptacopan	31	31	0.326 (0.270, 0.393)	-66.4 (-74.0, -56.6)
	Placebo	35	35	0.972 (0.815, 1.158)	
Day 360	Iptacopan	31	31	0.335 (0.279, 0.403)	N/A
	Placebo-iptacopan switch	35	33	0.339 (0.284, 0.405)	
Urinary sC5b-9/creatinine (pg/nmol)					
Day 180	Iptacopan	31	31	0.120 (0.072, 0.199)	-81.6 (-91.0, -62.3)
	Placebo	32	32	0.648 (0.392, 1.071)	
Day 360	Iptacopan	31	30	0.164 (0.093, 0.287)	N/A
	Placebo-iptacopan switch	32	30	0.148 (0.085, 0.259)	

I/Cs handled with a treatment policy strategy. Log transformed ratio to baseline was analysed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as an interaction term and log (baseline biomarker value) as a covariate. Correlations between visits within patients were modelled using an unstructured covariance matrix. The log transformation used refers to the natural log (base of e). Results were back-transformed and expressed as geometric means. ^aProportion of values outside limits of quantification >20% for both treatment groups at all visits, model estimates may be biased.

Abbreviations: b.i.d., twice daily; C3, complement component 3; CI, confidence interval; FAS, full analysis set; I/C, intercurrent events; MMRM, Mixed Model of Repeated Measures; n, number of patients with values non-missing and non-missing baseline at the designated visit; N: number of all patients included in the analysis (with non-missing baseline and covariates, N/A, not applicable).

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 14.2-7.3 and Table 14.2-7.3a).³³

2.5 Supportive clinical efficacy results

Supportive evidence for the clinical efficacy of iptacopan for the treatment of patients with C3G is provided by the Phase 2 study (Section 2.5.1) and the open-label extension study (Section 2.5.2).^{34, 38} The Phase 2 study included patients with post-transplant recurrence of C3G and is therefore summarised in the submission to provide data on this cohort, as APPEAR-C3G only included native kidney patients.³⁴ The open-label extension study is included to provide data on the long-term clinical efficacy and safety of iptacopan in C3G, as it represents the longest follow-up period in the clinical trial programme for iptacopan in C3G.³⁸

2.5.1 Phase 2 study

2.5.1.1 Summary of methodology

The Phase 2 study (NCT03832114) was an international, multicentre, open-label, single-arm, non-randomised study in adults with biopsy-confirmed C3G. The study included two cohorts of patients, one with native kidney C3G (native kidney cohort; Cohort A) and one with C3G recurrence following kidney transplantation (post-transplant recurrent cohort; Cohort B). All patients received iptacopan twice daily for 12 weeks. A total of 27 patients were enrolled and completed the study: 16 in the native kidney cohort and 11 in the post-transplant recurrent cohort.³⁷

A summary of the methodology of the Phase 2 study is provided in Table 22.

Table 22: Summary of methodology: Phase 2 study

Parameter	Phase 2 study (NCT03832114)
Study design	Multicentre, open-label, two cohort, single-arm, non-randomised Phase 2 study
Location	9 sites across 6 countries: UK (2 sites; 8 patients), France, Germany, Italy, Spain, US
Key eligibility criteria for patients	Native kidney cohort, N=16 (Cohort A): - Adult patients, ≥18 years of age - C3G confirmed by biopsy within 12 months prior to enrolment - On a maximum recommended or tolerated dose of ACEi or ARB for at least 30 days prior to treatment start - Any antiproteinuric medication at a stable dose prior to treatment start was allowed - MMF maintained on a stable dose for at least 30 days prior to treatment start - CS maintained on a stable dose (prednisolone ≤7.5 mg/day or equivalent) for at least 90 days prior to treatment start - UPCR ≥100 mg/mmol sampled from first morning void (or ≥1 g/24h total urinary protein excretion from a 24h urinary collection during run-in) at run-in or at baseline - eGFR (using the CKD-EPI formula)¹³¹ ≥30mL/min/1.73m² - Reduced C3 at screening (<0.90x lower limit of the lab normal ranges) - Vaccination against <i>N. meningitidis</i>, <i>S. pneumoniae</i> and <i>H. influenzae</i> at least 4 weeks prior to treatment start Post-transplant recurrent cohort, N=11 (Cohort B): - Adult patients, ≥18 years of age - C3G recurrence after kidney transplantation confirmed by biopsy after transplantation within 12 months prior to enrolment - eGFR (using the CKD-EPI formula)¹³¹ ≥30 mL/min/1.73m² - Normal or elevated urinary protein excretion - Vaccination against <i>N. meningitidis</i>, <i>S. pneumoniae</i> and <i>H. influenzae</i> at least 4 weeks prior to treatment start - On a stable dose of immunosuppression - Transplantation of a kidney allograft >90 days before screening - No signs of allograft rejection
Trial drug	Intervention: Iptacopan

Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

Parameter	Phase 2 study (NCT03832114)
	Treatment period 1 (12 weeks): • Dose escalation phase (Weeks 1–4) ◦ Week 1: Iptacopan 10 mg b.i.d. ◦ Week 2: Iptacopan 25 mg b.i.d. ◦ Week 3: Iptacopan 100 mg b.i.d. ◦ Week 4: Iptacopan 200 mg b.i.d. • Weeks 5–12 ◦ Iptacopan 200 mg b.i.d. was administered for an additional eight weeks, for a total duration of nine weeks Treatment period 2: • If patients entered treatment period 2, iptacopan 200 mg b.i.d. was administered for a further 12 weeks, for a total duration of 21 weeks at the highest dose • Dose levels were tapered down in two steps before treatment ended
Primary endpoint(s)	• Native kidney cohort: Ratio to baseline in UPCR derived from 24-hour urine collection at Week 12 • Post-transplant recurrent cohort: CfB to Week 12 in C3 deposit score based on immunofluorescence microscopy of kidney biopsy tissue
Secondary endpoints	• Biomarker levels of blood Bb • 24h urine UPCR and UACR • Change in and evolution of urinary albumin, urinary protein excretion, UACR, UPCR, serum creatinine, eGFR, creatinine clearance, haematuria • C3 level • Safety and tolerability • Plasma and urine PK assessments • Ratio to baseline of UPCR and UACR (post-transplant recurrent cohort only)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; b.i.d., twice daily; Bb, cleaved Factor b; C3, complement 3; C3G, complement 3 glomerulopathy; CfB, change from baseline; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; CS, corticosteroid; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PK, pharmacokinetics; RCT, randomised clinical trial; UACR, urine albumin-to-creatinine ratio; UK, United Kingdom; UPCR, urine protein-to-creatinine ratio; US, United States.

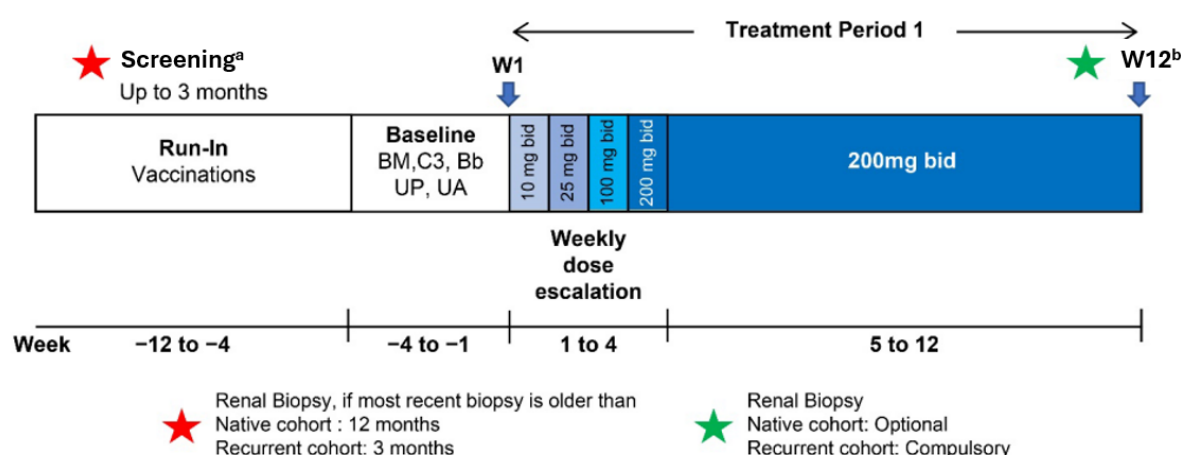
Sources: Wong et al. 2023;³⁷ Novartis Data on File. 2022 (CLNP023X2202 Phase 2 Clinical Study Report v1.0);³⁴ ClinicalTrials.gov (NCT03832114).¹²³

2.5.1.2 Trial design

The Phase 2 study included a screening period comprised of run-in (≤60 days) and a 30-day baseline period. Patients then entered treatment period 1, lasting 12 weeks, with dose escalation of iptacopan up to 200 mg b.i.d. (Figure 17). At Week 12, kidney biopsies were collected; these were optional for the native kidney cohort and mandatory for the post-transplant recurrent cohort.³⁴

Following 12 weeks of treatment in the Phase 2 study, patients could roll over to the extension study (NCT03955445) if treatment continuation was found to be beneficial by the investigator. If continuation of treatment was not deemed beneficial by the investigator, study medication was titrated down to 25 mg once daily for 7 days, followed by 10 mg once daily for a further 7 days. The patient then continued in the follow-up period (12 weeks) until the end-of-study visit.³⁴

Figure 17: Phase 2 study design



^aRun-in period could be extended to ensure stable doses of ACEi/AB, MMF, and or CS. ^bPatients may roll over into a separate extension study at Week 12

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Bb, cleaved factor b; b.i.d., twice daily; BM, biomarkers; C3, component C3; CS, corticosteroid; MMF, mycophenolate mofetil; UA, urinary albumin; UP, urinary protein; W, week

Source: Wong et al. 2023.³⁷

Patient disposition

A total of 27 patients (16 patients in the native kidney cohort and 11 patients in the post-transplant recurrent cohort) were enrolled and treated with iptacopan. All 27 patients (100%) completed the 12-week study and there were no discontinuations.³⁷

Twenty-six patients (96.3%) rolled over into the open-label extension study (NCT03955445) to continue long-term iptacopan treatment. One patient in the post-transplant recurrent cohort did not roll over and completed the tapering down and the follow-up period.³⁷

Baseline demographics and characteristics

Patients enrolled in the post-transplant recurrent cohort were on average older than patients in the native kidney cohort, with lower mean UPCR and eGFR at baseline. Key baseline demographics and disease characteristics for the Phase 2 patients are presented in Table 23.³⁴

Table 23: Phase 2 study baseline demographics and disease characteristics

	Native kidney cohort (N=16)	Post-transplant recurrent cohort (N=11)
Baseline demographics		
Age (years), Mean (SD)	26.1 (10.57)	34.5 (18.32)
Gender, n (%)		
Male	10 (63)	8 (73)
Female	6 (38)	3 (27)
Race, n (%)		
Caucasian	16 (100)	9 (82)
Black or African American	-	1 (9)
American Indian or Alaska Native	-	1 (9)
Baseline disease characteristics		
UPCR, Mean (SD)		
24h UPCR (g/mol)	454.0 (242.16)	112.3 (178.05)
eGFR (mL/min/1.73 m²), Mean (SD)	70.1 (35.10)	52.2 (17.29)
C3 deposit score,^a Median (range) (n)	-	3.0 (0.0–12.0) [n=10]
Concomitant therapy, n (%)		
ACEi	12 (75.0)	4 (36.4)
ARB	4 (25.0)	2 (18.2)
MPA (MMF or MPS)	5 (31.3)	9 (81.8)
CS	3 (18.8)	9 (82.0)
Calcineurin inhibitors	0	11 (100.0)

^aBaseline kidney biopsy was collected during the run-in period if the most recent biopsy was older than 3 months. Data are presented as mean (SD) unless stated otherwise. For all 24-hour urine collection parameters, baseline was defined to be the collection on Day –1 to Day 1. For eGFR, baseline was defined to be the last available assessment prior to the first dose of study drug. ^aBaseline kidney biopsy was collected during the run-in period if the most recent biopsy was older than 3 months.

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CS, corticosteroid; eGFR: estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPS, mycophenolate sodium; N: total number of patients; n: number of patients; SD, standard deviation; UPCR: urinary protein-to-creatinine ratio.

Sources: Wong et al. 2023;³⁷ Novartis Data on File. 2022 (CLNP023X2202 Phase 2 Clinical Study Report v1.0; Table 14.3–6.4).³⁴

2.5.1.3 Statistical analysis and definition of study groups

Sample size calculation was performed assuming that 15 patients in the native kidney cohort and 12 in the post-transplant recurrent cohort would provide 93% power for demonstration of true treatment reduction in log-transformed UPCR of 40% (SD 0.6) in the native kidney cohort, and 94% power for demonstration of true treatment reduction in C3 deposit score of 2 (SD 2) in the post-transplant recurrent cohort, respectively, for statistical significance at a 1-sided 10% significance level accounting for a drop-out rate of 20% in the native kidney cohort and 17% in the post-transplant recurrent cohort.³⁷

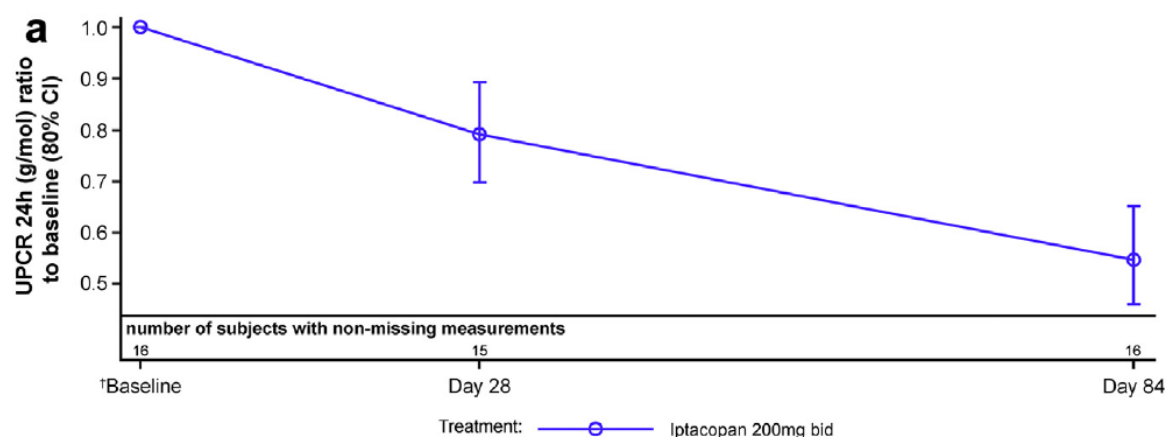
The log ratio of Week 12 to baseline in UPCR (primary endpoint in native kidney cohort) was analysed using an MMRM model. Change in C3 deposit score from baseline to Week 12 (primary endpoint in post-transplant recurrent cohort) was analysed using the Wilcoxon signed rank test to compare the median difference (80% CI).³⁷

2.5.1.4 Clinical effectiveness results

Native kidney cohort, primary endpoint: UPCR reduction at Week 12

In the native kidney cohort, treatment with iptacopan resulted in a 45% reduction in 24h UPCR from baseline (geometric mean: 401.9 g/mol) to Day 84 (geometric mean: 220.1 g/mol), with an adjusted geometric mean ratio of 0.55 (80% CI: 0.46, 0.65; 2-sided p=0.0003; see Figure 18).³⁷

Figure 18: UPCR (adjusted geometric mean [80% CI] of log ratio to baseline) in patients with native kidney C3G



Baseline is defined to be the 24-hour urine collection on Day -1 to Day 1.

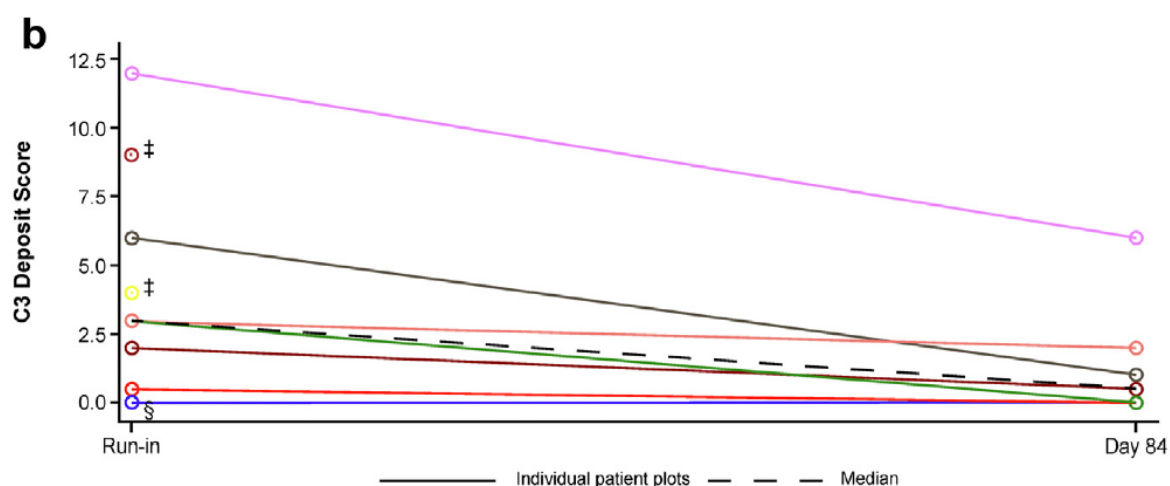
Abbreviations: C3G, complement 3 glomerulopathy; CI, confidence interval; UPCR, urine protein-to-creatinine ratio.

Source: Wong et al. 2023.³⁷

Post-transplant recurrent cohort, primary endpoint: CfB in C3 deposit score at Week 12

In the post-transplant recurrent cohort, treatment with iptacopan resulted in a significant decrease in median C3 deposit score in kidney biopsies from baseline (3.0) to Day 84 (0.5), with a median difference of -2.5 (80% CI: -3.75, -0.75; p=0.03). The individual C3 deposit scores as well as the median are presented in Figure 19. The analysis included data from all 7 patients in the post-transplant recurrent cohort with baseline and Day 84 biopsies available.³⁴

Figure 19: C3 total deposit score for patients with post-transplant recurrent C3G (individual plots; n=9)^a



^aA patient with recreational drug overdose was excluded from the analysis. [‡]Patients with only baseline values; Day 84 biopsy was either not taken or was damaged. [§]For patient represented by the blue line, the C3G recurrence was confirmed by the investigator based on a previous biopsy as per inclusion criteria.
Abbreviations: C3, complement component 3; C3G, complement 3 glomerulopathy; CI, confidence interval; UPCR, urine protein-to-creatinine ratio.
Source: Wong et al. 2023.³⁷

2.5.2 Open-label extension study

2.5.2.1 Summary of methodology

The open-label extension study (NCT03955445) is an ongoing, non-randomised study in patients receiving open-label iptacopan after completing treatment in APPEAR-C3G or the Phase 2 study.^{35, 38}

Table 24: Summary of methodology: Open-label extension study

Parameter	Open-label extension study (NCT03955445)
Study design	Open-label, non-randomised extension study
Location	33 sites across 17 countries: ³⁵ UK (3 sites; 9 patients originating from APPEAR-C3G and 8 patients originating from the Phase 2 study), Argentina, Brazil, Canada, China, Czechia, France, Germany, Greece, Israel, Italy, Japan, the Netherlands, Spain, Switzerland, Turkey, US
Eligibility criteria for patients	Patients must have completed the treatment period of APPEAR-C3G or the Phase 2 study on study drug. Please refer to Table 5 and Table 22 for information on eligibility criteria for APPEAR-C3G and the Phase 2 study, respectively.
Trial drug	Iptacopan 200 mg b.i.d.
Primary endpoints	<i>Patients originating from the native kidney cohort of the Phase 2 study:</i> Number of patients who achieve the composite renal endpoint at the 9-month visit (stable or improved eGFR [$\leq 10\%$ reduction] compared to the baseline visit in the Phase 2 study <i>and</i> either $\geq 50\%$ reduction in UPCR compared to baseline or reduction in UPCR to < 300 mg/g <i>and</i> either a $\geq 50\%$ increase in C3 compared to baseline or an increase in C3 to ≥ 90 mg/dL [i.e. $\geq$ the lower limit of normal]) <i>Patients originating from the post-transplant recurrent cohort of the Phase 2 study:</i> CfB in the C3 deposit score at the 6- to 9-month visit compared to the baseline visit in the Phase 2 study <i>All patients:</i> Long-term safety and tolerability of iptacopan
Secondary endpoints	Secondary endpoints are presented in Appendix J.2.2

Abbreviations: b.i.d., twice daily; C3G, complement 3 glomerulopathy; CfB, change from baseline; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio; US, United States.

Source: ClinicalTrials.gov (NCT03955445);³⁵ Novartis Data on File. 2023 (CLNP023B12001B Open-label Extension Study Clinical Study Report v1.0).³⁸

Patient disposition and treatment duration

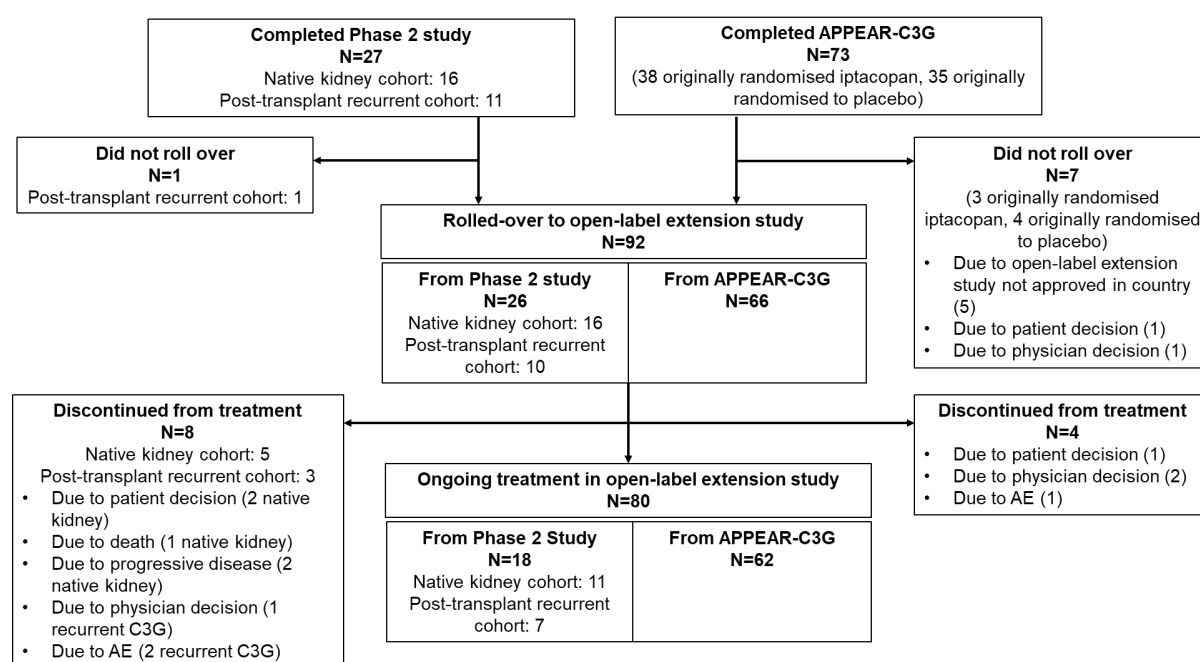
A total of 92 adult C3G patients entered the open-label extension study: 26 patients out of the 27 patients who had completed the Phase 2 study (16 patients with native kidney C3G and 10 patients with post-transplant recurrent C3G) and 66 patients out of the 73 patients who had completed APPEAR-C3G. As of the data cut-off date of 6th May 2024, 80 patients (18 from the Phase 2 study and 62 from APPEAR-C3G) were ongoing on treatment in the study (Figure 20).

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The overall 12 treatment discontinuations were due to patient decision (n=3), physician decision (n=3), adverse event (AE) (n=3), progressive disease (n=2), and death (n=1).¹²⁴

At the time of data cut-off, among the 26 patients who entered the extension study from the Phase 2 study, 22 patients had ≥ 2 years of treatment, 20 patients had ≥ 3 years of treatment, and 13 patients had ≥ 4 years of iptacopan treatment. The mean duration of treatment was 3.6 years (SD: 1.2 years). Among the 66 patients who entered the extension study from APPEAR-C3G, 53 (71.6%) completed the 15-month visit, 36 (48.6%) completed the 18-month visit, 27 (36.5%) completed the 21-month visit and 13 (17.6%) completed the 24-month visit at the time of data cut-off.¹²⁴

Figure 20: Disposition of patients originating from the Phase 2 study and APPEAR-C3G in the open-label extension study (CONSORT diagram)



Abbreviations: AE, adverse event; C3G, Complement 3 glomerulopathy; N, total number of patients.

Source: Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 1; Table 1-1.1.4 and Table 1-1.1.3)¹²⁴

Baseline demographics and characteristics

Demographics and baseline disease characteristics for patients entering the open-label extension study are presented in Appendix J.3.4.¹²⁴

2.5.2.2 Clinical effectiveness results for open-label extension study

The presentation of clinical effectiveness results from the open-label extension study in this section focuses on long-term data for UPCR and eGFR as the most clinically relevant outcomes. Further results are presented in Appendix J.3.5.²⁷

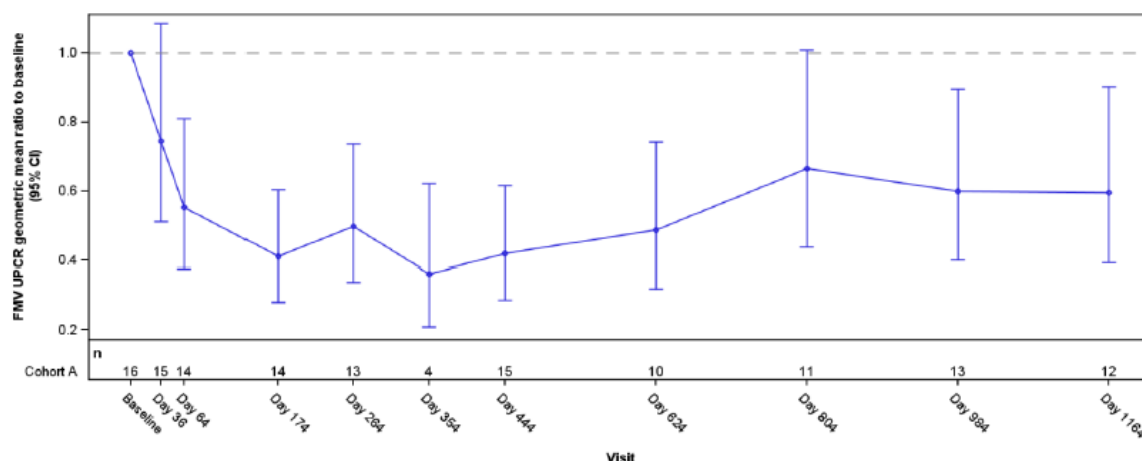
CfB in FMV UPCR – extension study data for patients originating from the Phase 2 study

In patients originating from the Phase 2 study native kidney cohort with a geometric mean FMV UPCR of 2.66 g/g at baseline, a reduction in FMV UPCR with iptacopan treatment was observed early and sustained up to Day 1,164 (Figure 21). FMV UPCR reduction at Day 1,164 amounted to 40%.³⁸

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In the post-transplant recurrent cohort, the FMV UPCR values were within the normal range (<0.2 g/g) for most participants at baseline. In 4 out of 7 participants with available FMV UPCR measurements at Day 1,164, these values remained within the normal range, one participant had UPCR just above the normal range, and in the other two participants the UPCR remained well controlled with values of approximately 0.3 g/g.³⁸

Figure 21: Model-estimated geometric mean ratio to baseline of FMV UPCR over time in patients originating from the Phase 2 native kidney cohort



Log-transformed ratio to baseline was analysed using a MMRM model. The model included timepoint (as study day relative to the date of first administration of study treatment) as a fixed effect, and the extension study log-transformed baseline measurement as fixed covariate. Timepoint was included as a repeated factor with an autoregressive covariance matrix to allow adjustment for correlations between timepoints within participants. Baseline is defined to be the last non-missing FMV assessment prior to the date of first administration of study drug in the extension study.

Visits on Days 174, 264, 354, 444, 624, 804, 984, 1164 correspond to 3, 6, 9, 12, 18, 24, 30, 36 months in the extension study.

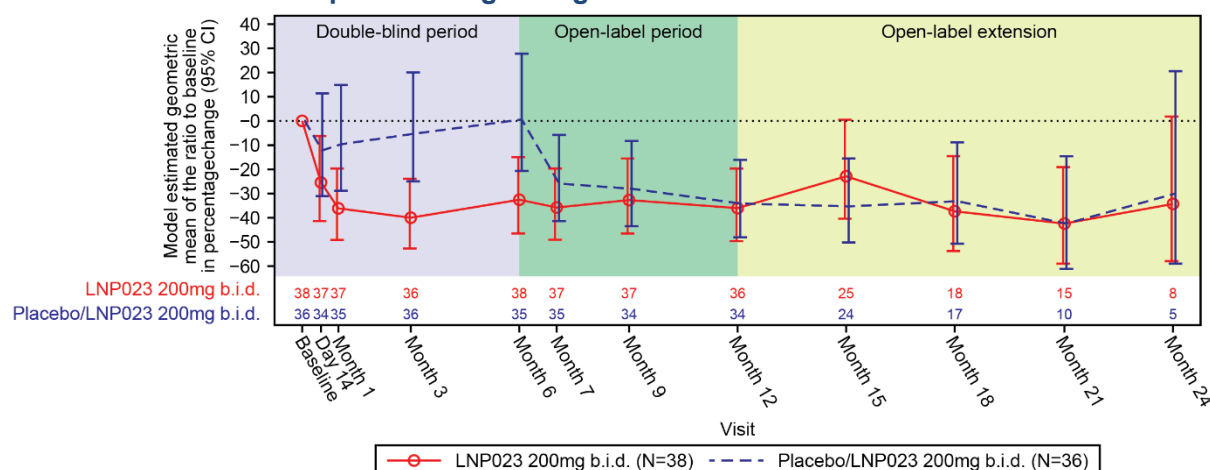
Abbreviations: CI, confidence interval; FMV, first morning void; MMRM, Mixed Model of Repeated Measures; n: number of participants with non-missing measurements; UPCR, urine protein-to-creating ratio

Source: Novartis Data on File. 2024 (Open-label extension study; clinical study report; 36-month interim analysis; Figure 11-4).³⁸

CfB in FMV UPCR – extension study data for patients originating from APPEAR-C3G

In patients who were originally randomised to the iptacopan arm in APPEAR-C3G, the reduction from baseline in FMV UPCR was sustained in the open-label extension study up to 24 months. For patients who were originally randomised to the placebo arm, a similar reduction in FMV UPCR was observed after switch to iptacopan in the open-label period of the APPEAR-C3G trial (Month 6–Month 12). This reduction was sustained up to Month 24. The full measures of CfB in FMV UPCR up to Month 24 are presented in Figure 22.¹²⁴

Figure 22: Model-estimated geometric mean ratio to baseline in percentage change of UPCR FMV over time in patients originating from APPEAR-C3G



Bars represent 95% confidence intervals. Log transformed ratio to baseline was analysed using an MMRM which included treatment, visit, and stratification variable as fixed effects, treatment*visit as an interaction term and log (baseline UPCR FMV) as a covariate.

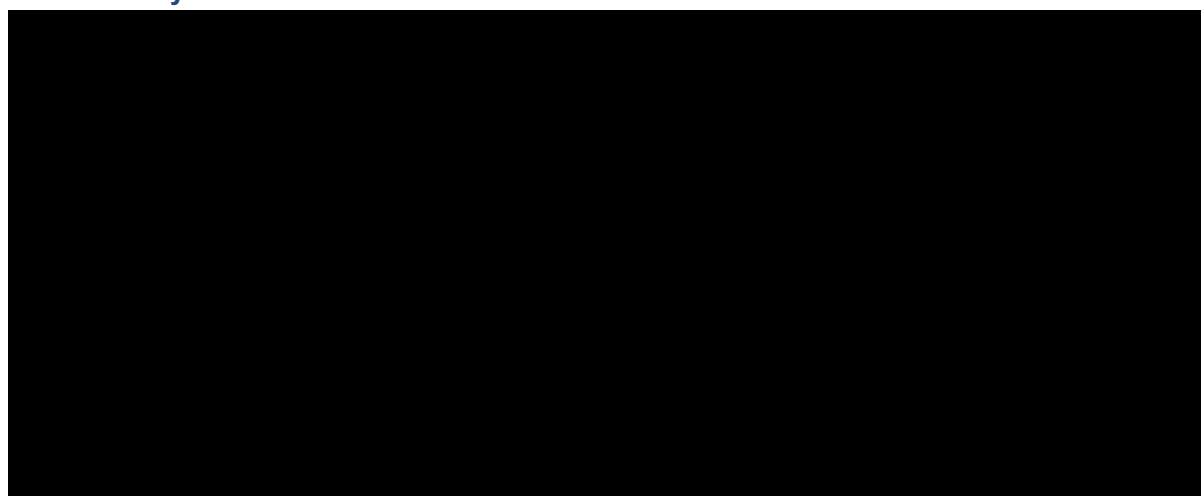
Abbreviations: b.i.d., twice daily; CI, confidence interval; FMV, first morning void; UPCR, urinary protein-to-creatinine ratio.

Source: Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 2; Figure 3-1).¹²⁴

Change in eGFR slope analysis – extension study data for patients originating from the Phase 2 study

In the native kidney cohort, historical eGFR data were available for 13 of 16 patients, with a median of 4 historical eGFR values (range 1–10). All 16 patients had on-iptacopan eGFR data. The pre-iptacopan annualised eGFR slope was $-13.43 \text{ mL/min/1.73m}^2/\text{year}$ (95% CI: $-20.36, -6.51$). The annualised eGFR slope upon initiation of iptacopan was estimated as $-2.08 \text{ mL/min/1.73m}^2/\text{year}$ (95% CI: $-11.34, 7.18$), representing a change in the eGFR trajectory of $11.35 \text{ mL/min/1.73m}^2/\text{year}$ in annualised eGFR compared to the pre-iptacopan period (95% CI: $3.30, 19.41$; $p=0.0089$; Figure 23).³⁸

Figure 23: Change in annualised eGFR slope in patients originating from the Phase 2 native kidney cohort



Participant [redacted] eGFR value at extension Day 90 appeared to be due to a measurement error and was omitted from the Day 174 visit (extension Day 94 was used in the Day 174 visit).

Study visits are Days 174, 264, 354, 444, 624, 804, 984, 1164 (3, 6, 9, 12, 18, 24, 30, 36 months in the extension).

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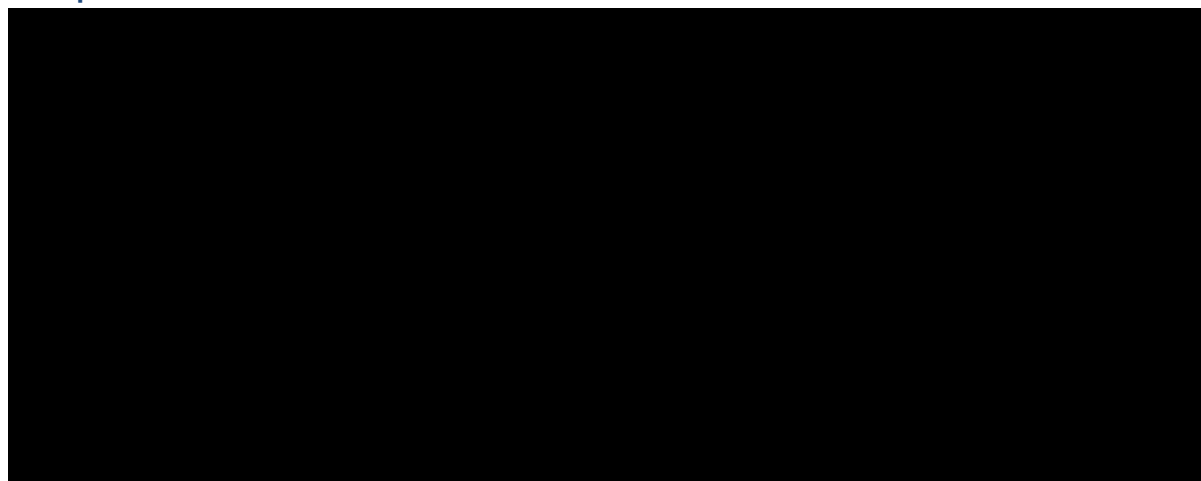
The blue shaded area is 95% CI and the thick blue line is predicted fit.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; n, number of participants with non-missing measurements.

Source: Novartis Data on File. 2024 (Open-label extension study; clinical study report; 36-month interim analysis; Figure 11-7).³⁸

In the post-transplant recurrent cohort, the historical eGFR data collected as part of the trial included values prior to the diagnosis of C3G recurrence in each patient's most recent kidney transplant. Therefore, the available pre-iptacopan eGFR data do not reflect the disease course for patients following C3G recurrence. Ten participants had on-iptacopan eGFR data and the annualised eGFR slope upon initiation of iptacopan was estimated as [REDACTED] mL/min/1.73m²/year (95% CI: [REDACTED]). Given the small sample size, the estimate is sensitive to eGFR changes in individual patients. Among the 10 patients included in the analysis, two patients exhibited progressive graft dysfunction due to acute kidney injury and worsening of recurrent C3G, respectively, and discontinued the study, while one patient (who was still in the study at the cut-off date) had a decline in eGFR for reasons other than C3G recurrence.³⁸

Figure 24: Individual time profiles of eGFR in patients originating from the Phase 2 post-transplant recurrent cohort



Participant [REDACTED] discontinued iptacopan treatment on Day 179.

Visits on days 174, 264, 354, 444, 624, 804, 984, 1164 correspond to 3, 6, 9, 12, 18, 24, 30, 36 months in the extension study.

Participants with C3GN are presented with dash line and with DDD are presented with solid line. Participant [REDACTED] had missing disease sub-type.

Abbreviations: C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate

Source: Novartis Data on File. 2024 (Open-label extension study; clinical study report; 36-month interim analysis; Figure 11-8).³⁸

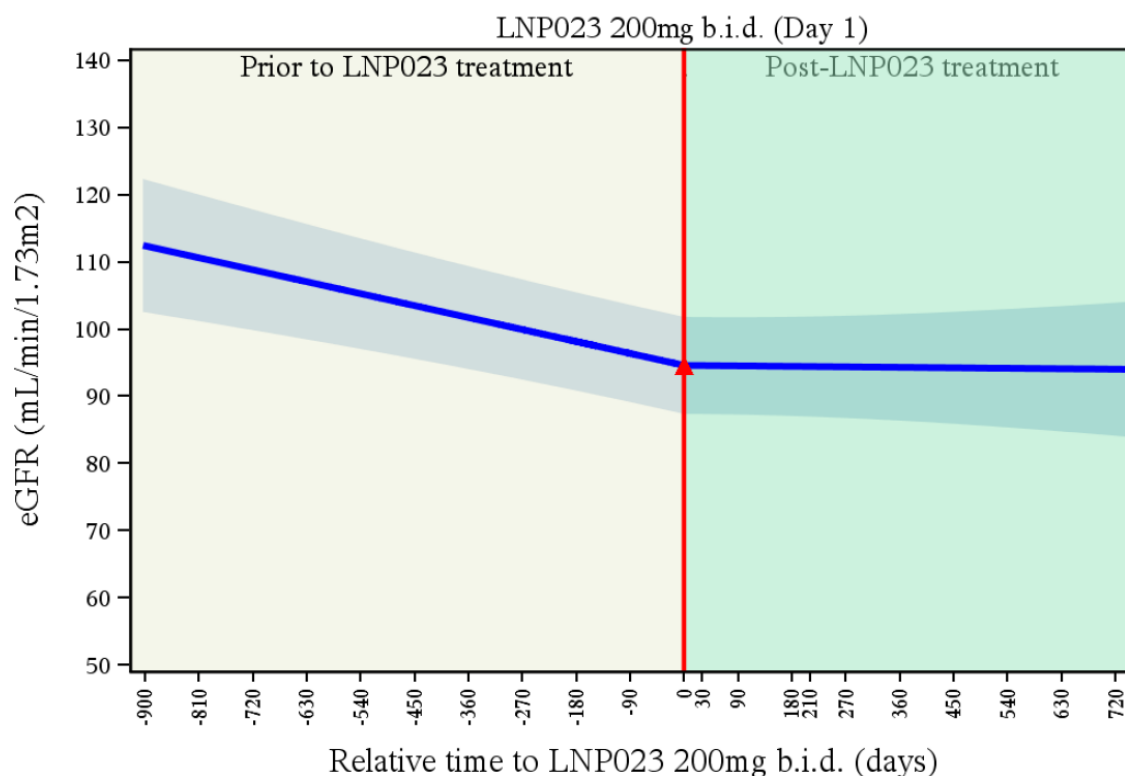
Change in eGFR slope analysis – extension study data for patients originating from APPEAR-C3G

Methods for the eGFR slope analysis in the APPEAR-C3G population are described in Section 2.4.3.2 ('Exploratory endpoint: eGFR slope change analyses'). The eGFR slope analysis in patients originating from APPEAR-C3G including data from the extension study was informed by 74 patients contributing data for the calculation of the pre-iptacopan slope as well as the on-iptacopan slope. The pre-iptacopan slope was estimated based on 494 eGFR measurements, while 564 eGFR measurements were available for estimation of the on-iptacopan slope. Among the 74 patients included in the analysis, 73 (98.6%) had completed 12 months of iptacopan treatment and 36 (48.6%) had completed 18 months of iptacopan treatment at the time of analysis.¹²⁴

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The mean pre-iptacopan eGFR slope was $-7.22 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $-10.10, -4.35$). Treatment with iptacopan led to stabilisation of the eGFR decline, with the on-iptacopan slope estimated as $-0.29 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $-3.88, 3.31$). This equated to a change in annual eGFR slope of $6.94 \text{ mL/min/1.73 m}^2$ (95% CI: $3.48, 10.39$; $p=0.0001$) compared with pre-iptacopan treatment (Figure 25).¹²⁴

Figure 25: eGFR slope change with iptacopan treatment – APPEAR-C3G patients including extension study data (n=74)



Number of patients: 74. The x-axis represents the relative study day to iptacopan (LNP023) treatment. eGFR slopes per year were analysed using a linear mixed effects model including time (analysis day before or after change point [Day 1 of iptacopan treatment]) as a continuous covariate, patient-level intercept and slope (time) as random effects.

Abbreviations: b.i.d., twice daily; eGFR, estimated glomerular filtration rate

Source: Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 1; Figure 2-1.2).¹²⁴

2.6 Subsequent treatments used in the relevant studies

Information on subsequent treatments for patients discontinuing iptacopan was not systematically collected in the clinical trials. In the economic model, patients who discontinued iptacopan were assumed to receive SoC alone (see Section 3.3.3).

2.7 Subgroup analysis

This submission covers the full population of the planned marketing authorisation in C3G.

The pre-specified subgroup analyses conducted for the primary endpoint of APPEAR-C3G are presented in Section 2.4.3. This includes a subgroup analysis for people with C3GN and DDD; however, interpretability of results is limited by the small sample size and imbalance between groups (DDD patients in iptacopan arm $n=9$, placebo arm $n=1$).³³

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Whilst a distinction between C3GN and DDD is made based on kidney tissue biopsy findings,¹³³ the clinical presentation, disease course, and management of these C3G subtypes are generally considered to be consistent.^{5, 18, 19, 43} Consequently, the clinical and cost-effectiveness of iptacopan are not expected to differ between people with C3GN and DDD.⁴⁰ Similarly, CFHR5 nephropathy is a subtype of C3GN, caused by a genetic mutation endemic to people of Cypriot origin,^{44, 45} and clinical and cost-effectiveness of iptacopan are not expected to differ from other people with C3G.

Evidence for the clinical efficacy of iptacopan in patients with post-transplant recurrence of C3G is presented in Section 2.5.1 (12-week data from Phase 2 study)³⁴ and Section 2.5.2 (longer-term data from extension study).³⁸

Economic modelling is based on iptacopan trial data from patients with native kidney C3G, based on APPEAR-C3G.³³ For patients with post-transplant recurrence, the sample size of the Phase 2 clinical trial cohort (N=11) did not permit a robust economic analysis.³⁴ However, given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients.^{27, 40} Furthermore, the approach to model only a native kidney population aligns with that taken in previous NICE appraisals in other chronic kidney diseases, with the NICE recommendations for these treatments not excluding transplanted patients even where transplanted patients were excluded from the clinical trials. Further details are provided in Table 12 of Appendix E.

2.8 Meta-analysis

In order to leverage all available data, including for a scenario analysis used in the economic model (Section 3.3.2), an exploratory analysis pooling data across trials was conducted for the eGFR slope outcome. Results of this analysis are presented below in Section 2.8.1.

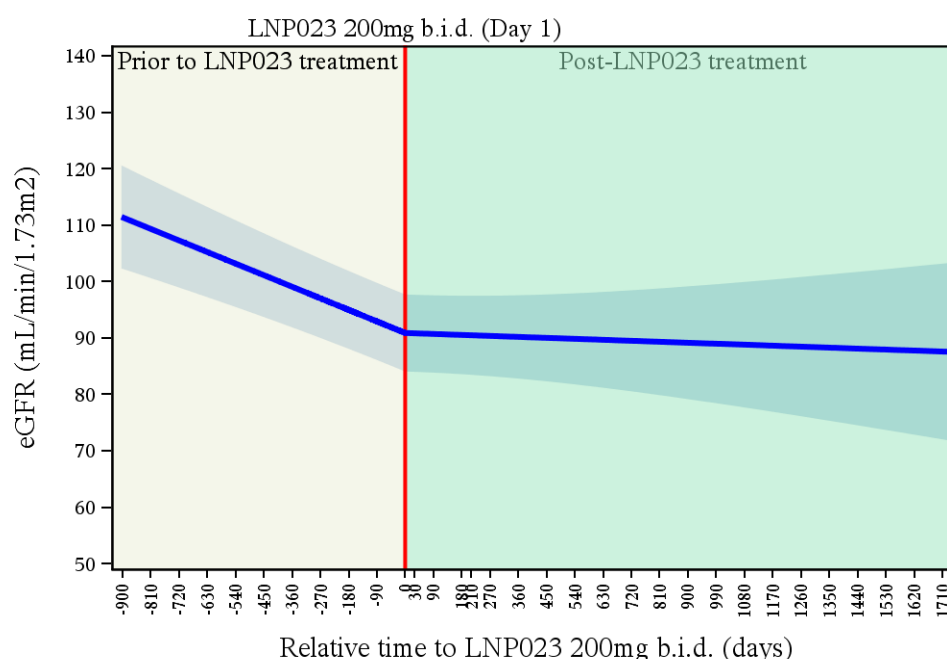
In addition, iptacopan safety data were summarised across trials (broad safety set) and are presented in Section 2.10.

2.8.1 Pooled eGFR slope analysis

An exploratory analysis pooled eGFR data across APPEAR-C3G, the Phase 2 trial (native kidney cohort) and the open-label extension study. This analysis maximises data availability for the estimation of eGFR slope in terms of sample size and length of follow-up. Overall, 90 patients with native kidney C3G contributed data to the pre-iptacopan slope as well as the on-iptacopan slope, with a total of 596 eGFR measurements informing the pre-iptacopan and 828 informing the on-iptacopan slope, respectively. Among the 90 patients, 72 (80.0%) were on iptacopan for at least 12 months at the time of analysis, and 38 patients (42.2%) were on iptacopan for at least 18 months.¹²⁴

Across the pooled data, the mean pre-iptacopan eGFR slope was $-8.32 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $-10.89, -5.74$). Treatment with iptacopan led to stabilisation of eGFR decline, with the on-iptacopan slope estimated as $-0.70 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $-3.77, 2.36$); consequently, the change in annualised eGFR slope following initiation of iptacopan treatment versus pre-iptacopan treatment was $7.62 \text{ mL/min/1.73 m}^2$ (95% CI: $4.62, 10.62$; $p < 0.0001$; Figure 26).¹²⁴

Figure 26: eGFR slope change with iptacopan treatment – native kidney C3G patients in pooled studies including extension study data (n=90)



Number of patients: 90. x-axis represents the relative study day to iptacopan (LNP023) treatment. eGFR slopes per year were analysed using a linear mixed effects model including time (analysis day before or after change point [Day 1 of iptacopan treatment]) as a continuous covariate, patient-level intercept and slope (time) as random effects.

Source: Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 1; Figure 2-1.1).¹²⁴

2.9 Indirect and mixed treatment comparisons

The APPEAR-C3G trial and the historical eGFR analyses presented in previous sections are considered to provide a robust source of SoC data in C3G. Background medications received by the patient population in APPEAR-C3G were considered reflective of UK clinical practice by clinicians.²⁷ Therefore, data from APPEAR-C3G (including historical data) were deemed suitable to inform the comparison of iptacopan with established clinical management (SoC comparator) in the economic model.

Comparative data versus eculizumab were not available from the iptacopan clinical trial programme in C3G. Whilst eculizumab is considered of limited relevance as a comparator for this submission (for reasons described in Table 1), the feasibility of an indirect treatment comparison (ITC) was assessed for completeness. The clinical trials SLR (Appendix B) identified three trials which assessed eculizumab for C3G. However, none of the three studies reported eGFR results, the outcome of interest for the economic model (see Section 3.3.2.1). In addition, sample sizes were small, ranging from 4–6 patients across each of the three trials. None of the studies were conducted in the UK, and thus did not reflect the patient population who is eligible to receive eculizumab under the NHS England commissioning policy criteria.²⁸ Overall, an ITC was not considered feasible. Further details of the ITC feasibility assessment are described in Appendix B.1.7.

2.10 Adverse reactions

The safety data presented in this section cover the placebo-controlled period of the APPEAR-C3G trial, as well as all available safety data pooled across APPEAR-C3G, the Phase 2 study, and the ongoing open-label extension study for iptacopan in C3G. Two safety sets are presented below:

- The **controlled safety set (N=74)** includes data from the 6-month double-blind placebo-controlled period of APPEAR-C3G from all adult patients who received at least one dose of iptacopan 200 mg b.i.d. (N=38) or placebo (N=36)¹²⁵
- The **broad safety set (N=101)** includes data from all adult patients who received at least one dose of iptacopan 200 mg b.i.d. in the treatment period of any of the three iptacopan studies in C3G (Phase 2, APPEAR-C3G, and the ongoing open-label extension study), up to the data cut-off date of 6th May 2024¹²⁵

2.10.1 Summary of adverse events

In the controlled safety set, AEs were overall balanced between the iptacopan and placebo arms. The number of patients with treatment-emergent adverse events (TEAEs) reported during the 6-month double-blind period was comparable between the iptacopan (30/38, 78.9%) and placebo (24/36, 66.7%) arms. Iptacopan was well tolerated with the majority of AEs being mild to moderate in severity. A low number of serious adverse events (SAEs) was reported and there were no deaths. Iptacopan was well tolerated with the majority of AEs being mild to moderate in severity. No patients discontinued treatment due to AEs.¹²⁵

In the broad safety set, with 189.8 patient-years (PYs) of iptacopan 200 mg b.i.d. exposure overall, the proportion of patients who had at least one TEAE was 85.1% (86/101). There was no evidence of increased risk of TEAEs with longer exposure. The exposure-adjusted occurrence rate (defined as the number of AE episodes/100 PYs of exposure) was 266.5 episodes/100 PYs in the broad safety set, which was lower than that in the iptacopan group of the controlled safety set (431.8 episodes/100 PYs). One death was reported (not suspected to be related to iptacopan), and three patients discontinued iptacopan due to AEs.¹²⁵

A summary of AEs is presented in Table 25, with further details provided in the following sections.

Table 25: Summary of adverse events in controlled safety set and broad safety set

	Controlled safety set		Broad safety set
	Iptacopan 200 mg b.i.d. (N=38)	Placebo (N=36)	Iptacopan 200 mg b.i.d. (N=101)
Number of patients, n (%)			
TEAEs	30 (78.9)	24 (66.7)	86 (85.1)
TEAEs suspected to be related to study treatment	7 (18.4)	4 (11.1)	23 (22.8)
SAEs	3 (7.9)	1 (2.8)	20 (19.8)
SAEs suspected to be treatment-related	1 (2.6)	0	4 (4.0)
Severe AEs	2 (5.3)	1 (2.8)	12 (11.9)

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	Controlled safety set		Broad safety set
	Iptacopan 200 mg b.i.d. (N=38)	Placebo (N=36)	Iptacopan 200 mg b.i.d. (N=101)
Deaths	0	0	1 (1.0)
Treatment discontinuations due to AEs	0	0	3 (3.0)
Dose reductions or interruptions due to AEs	4 (10.5)	4 (11.1)	11 (10.9)

Abbreviations: AE, adverse event; b.i.d., twice daily; n, number of patients with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: Novartis Data on File, 2024 (Summary of Clinical Safety in C3 glomerulopathy; v1.0 Table 2-1).¹²⁵

2.10.2 Treatment-emergent adverse events

The total incidence of TEAEs during the double-blind phase in patients treated with iptacopan was 78.9%, compared with 66.7% among patients receiving placebo. The incidence of TEAEs in the broad safety set was 85.1%. A summary of TEAEs occurring in ≥5% of any treatment group is presented in Table 26.¹²⁵

Table 26: Summary of TEAEs (≥5% in any treatment group)

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients, n (%)			
Number of patients with at least one event	30 (78.9)	24 (66.7)	86 (85.1)
COVID-19	8 (21.1)	6 (16.7)	30 (29.7)
Blood creatine phosphokinase increased	5 (13.2)	1 (2.8)	11 (10.9)
Nasopharyngitis	4 (10.5)	1 (2.8)	14 (13.9)
Headache	2 (5.3)	1 (2.8)	9 (8.9)
Cough	2 (5.3)	1 (2.8)	8 (7.9)
Anaemia	2 (5.3)	0	6 (5.9)
Upper respiratory tract infection	2 (5.3)	0	6 (5.9)
Blood creatinine increased	2 (5.3)	0	5 (5.0)
Otitis media	2 (5.3)	0	5 (5.0)
Aspartate aminotransferase increased	2 (5.3)	0	3 (3.0)
Respiratory tract infection viral	2 (5.3)	0	3 (3.0)
Vomiting	1 (2.6)	1 (2.8)	8 (7.9)
Diarrhoea	1 (2.6)	0	7 (6.9)
Hyperkalaemia	1 (2.6)	0	6 (5.9)
Nausea	1 (2.6)	2 (5.6)	4 (4.0)
Hypercholesterolaemia	1 (2.6)	2 (5.6)	3 (3.0)
Renal impairment	0	0	6 (5.9)

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	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Vitamin D deficiency	0	1 (2.8)	6 (5.9)

Abbreviations: COVID-19, coronavirus disease; n, number of patients with at least one event; TEAE, treatment emergent adverse event.

Source: Novartis Data on File, 2024 (Summary of Clinical Safety in C3 glomerulopathy; v1.0 Appendix 1 Table 2-3).¹²⁵

In the controlled safety set, TEAEs suspected to be treatment-related were reported by the investigator in 18.4% and 11.1% of patients in the iptacopan and placebo groups, respectively. In the broad safety set, TEAEs suspected to be treatment-related were reported by the investigator in 22.8% of patients (Table 27).¹²⁵

Table 27: Summary of TEAEs suspected to be treatment-related

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients, n (%)			
Number of patients with at least one event	7 (18.4)	4 (11.1)	23 (22.8)
Blood creatine phosphokinase increased	1 (2.6)	0	2 (2.0)
Nausea	1 (2.6)	1 (2.8)	2 (2.0)
Aspartate aminotransferase increased	1 (2.6)	0	1 (1.0)
Blood culture positive	1 (2.6)	0	1 (1.0)
Cough	1 (2.6)	0	1 (1.0)
Dihydrotestosterone decreased	1 (2.6)	0	1 (1.0)
Headache	1 (2.6)	0	1 (1.0)
Lower respiratory tract infection	1 (2.6)	0	1 (1.0)
Otitis media	1 (2.6)	0	1 (1.0)
Pneumonia	1 (2.6)	0	1 (1.0)
Upper respiratory tract infection	1 (2.6)	0	1 (1.0)
Urinary tract infection	0	0	3 (3.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Abdominal pain	0	0	1 (1.0)
Acne	0	0	1 (1.0)
Acute respiratory distress syndrome	0	0	1 (1.0)
Adverse drug reaction	0	0	1 (1.0)

Abbreviations: TEAE, treatment emergent adverse event.

Source: Novartis Data on File, 2024 (Summary of Clinical Safety in C3 glomerulopathy; v1.0 Appendix 1 Table 2.1-5).¹²⁵

2.10.3 Serious adverse events

In the controlled safety set, SAEs were reported for three patients in the iptacopan group and one patient in the placebo group. In the broad safety set, SAEs were reported in 20 (19.8%)

patients treated with iptacopan, who experienced a total of 36 SAEs. Approximately half of SAEs were infection related. A full breakdown of SAEs is presented in Table 28.¹²⁵

Table 28: All SAEs reported

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients, n (%)			
Number of patients with at least one event	3 (7.9)	1 (2.8)	20 (19.8)
Blood culture positive ^a	1 (2.6)	0	1 (1.0)
Chest discomfort	1 (2.6)	0	1 (1.0)
Infected bite	1 (2.6)	0	1 (1.0)
Acute kidney injury	0	1 (2.8)	3 (3.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Acute left ventricular failure	0	0	1 (1.0)
Acute respiratory distress syndrome	0	0	1 (1.0)
Appendicitis	0	0	1 (1.0)
Arrhythmia	0	0	1 (1.0)
Atrial fibrillation	0	0	1 (1.0)
C3 glomerulopathy	0	0	1 (1.0)
Cardiac failure	0	0	1 (1.0)
Drug abuse	0	0	1 (1.0)
Enteritis	0	0	1 (1.0)
Gastroenteritis	0	0	1 (1.0)
Hyperkalaemia	0	0	1 (1.0)
Intervertebral discitis	0	0	1 (1.0)
Mallory-Weiss syndrome	0	0	1 (1.0)
Norovirus infection	0	0	1 (1.0)
Overdose	0	0	1 (1.0)
Pelvic inflammatory disease	0	0	1 (1.0)
Pericarditis	0	0	1 (1.0)
Pneumococcal sepsis	0	0	1 (1.0)
Pneumocystis jirovecii pneumonia	0	0	1 (1.0)
Pneumonia	0	0	1 (1.0)
Pyelonephritis	0	0	1 (1.0)
Renal impairment	0	0	1 (1.0)
Retroperitoneal haematoma	0	0	1 (1.0)
Septic shock	0	0	1 (1.0)
Streptococcal bacteraemia	0	0	1 (1.0)
Tendon rupture	0	0	1 (1.0)

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Upper gastrointestinal haemorrhage	0	0	1 (1.0)
Ascites	0	1 (2.8)	0

^aBlood culture positive for *Streptococcus pneumoniae*.

Abbreviations: n, number of patients with at least one event; SAE, serious adverse event.

Source: Novartis Data on File. 2024 (Summary of Clinical Safety in C3 glomerulopathy; v1.0 Appendix 1 Table 2.1-9).¹²⁵

In the controlled safety set, SAEs suspected to be treatment-related were reported in 2.6% and 0% of patients in the iptacopan and placebo groups, respectively. In the broad safety set, 9 SAEs suspected to be related to iptacopan treatment were reported in 4 patients (4.0% of 101 patients) (Table 29). Most treatment-related SAEs were infections, all of which were resolved or resolving at the time of data read-out.¹²⁵

Table 29: Summary of SAEs suspected to be treatment-related

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients, n (%)			
Number of patients with at least one event	1 (2.6)	0	4 (4.0)
Blood culture positive ^a	1 (2.6)	0	1 (1.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Acute respiratory distress syndrome	0	0	1 (1.0)
Norovirus infection	0	0	1 (1.0)
Pneumococcal sepsis	0	0	1 (1.0)
Pneumocystis jiroveci pneumonia	0	0	1 (1.0)
Septic shock	0	0	1 (1.0)
Streptococcal bacteraemia	0	0	1 (1.0)

^aBlood culture positive for *Streptococcus pneumoniae*.

Abbreviations: n, number of patients with at least one event; SAE, serious adverse event.

Source: Novartis Data on File. 2024 (Summary of Clinical Safety in C3 glomerulopathy; v1.0 Appendix 1 Table 2.1-11).¹²⁵

2.10.4 Deaths

One death occurred across the three C3G studies, during the open-label extension study. The cause of death was presumed to be cardiac arrhythmia that the investigator did not consider to be related to iptacopan.¹²⁵

2.10.5 Treatment discontinuations due to adverse events

No treatment discontinuations due to TEAEs were reported in the controlled safety set. In the broad safety set, three patients discontinued iptacopan treatment due to TEAEs during the ongoing open-label extension study. All three cases were due to SAEs not related to iptacopan treatment, as determined by the investigator.¹²⁵

In the controlled safety set, TEAEs leading to study treatment interruption were reported in 10.5% and 11.1% of patients in the iptacopan and placebo groups, respectively. The most frequently reported TEAE leading to interruption of iptacopan treatment was COVID-19 (reported in four patients, 10.5%).¹²⁵

In the broad safety set, TEAEs leading to study treatment interruption were reported in 10.9% of patients. In addition, one patient had a temporary dose reduction due to non-serious tonsillar hypertrophy.¹²⁵

2.10.6 Adverse events of special interest

The AEs of special interest for iptacopan were determined based on its mechanism of action, pre-clinical safety studies and clinical studies, and include infections caused by encapsulated bacteria, testicular effects, thyroid changes, malignancy, hypersensitivity, and decreased platelets.¹²⁵

In the controlled safety set, three patients in the iptacopan group and one patient in the placebo group were reported to have infections caused by encapsulated bacteria. Additionally, one patient in the placebo group experienced a non-serious TEAE of blood thyroid stimulating hormone increased.¹²⁵

In the broad safety set, 10 patients (including the three described above in the controlled safety set) were reported to have infections caused by encapsulated bacteria. Most patients had infections that were non-serious and not considered to be related to iptacopan treatment. All infections resolved and patients either continued iptacopan treatment or resumed after resolution of the infection. Additionally, eight patients reported AEs recorded as hypersensitivity, but these were not considered related to iptacopan treatment.¹²⁵

No AEs of special interest related to testicular effect, malignancy or decreased platelet count were reported in either safety population. A summary of AEs of special interest is presented in Table 30.¹²⁵

Table 30: Summary of AEs of special interest

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients with at least one event, n (%)			
Infections caused by encapsulated bacteria	3 (7.9)	1 (2.8)	10 (9.9)^c
<i>As per pre-defined search criteria</i>			
Otitis media	2 (5.3)	0	5 (5.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Cellulitis	0	0	1 (1.0)
Otitis media acute	0	0	1 (1.0)
Pneumococcal sepsis	0	0	1 (1.0)
Streptococcal bacteraemia ^a	0	0	1 (1.0)
Urethritis gonococcal	0	1 (2.8)	0

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	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Manual search^b			
Blood culture positive	1 (2.6)	0	1 (1.0)
Septic shock	0	0	1 (1.0)
Intervertebral discitis	0	0	1 (1.0)
Serious or severe infections	2 (5.3)	0	9 (8.9)
Blood culture positive	1 (2.6)	0	1 (1.0)
Infected bite	1 (2.6)	0	1 (1.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Appendicitis	0	0	1 (1.0)
Gastroenteritis	0	0	1 (1.0)
Intervertebral discitis	0	0	1 (1.0)
Norovirus infection	0	0	1 (1.0)
Pelvic inflammatory disease	0	0	1 (1.0)
Pneumococcal sepsis	0	0	1 (1.0)
<i>Pneumocystis jirovecii</i> pneumonia	0	0	1 (1.0)
Pneumonia	0	0	1 (1.0)
pyelonephritis	0	0	1 (1.0)
Septic shock	0	0	1 (1.0)
Streptococcal bacteraemia ^a	0	0	1 (1.0)
Hypersensitivity	0	0	8 (7.9)
Rash	0	0	5 (5.0)
Eczema	0	0	1 (1.0)
Hand dermatitis	0	0	1 (1.0)
Periorbital dermatitis	0	0	1 (1.0)
Rhinitis allergic	0	0	1 (1.0)
Thyroid changes	0	1 (2.8)	0
Blood thyroid stimulating hormone increased	0	1 (2.8)	0

^aAE was reported verbatim as septic shock (due to streptococcal bacteraemia). ^bManual search included serious/severe infection in SOC Infections and infestations and HLGT Microbiology and serology investigations.^c The total number of patients within the broad safety set with at least one event (n=10) includes otitis media (5 patients), otitis media acute (1 patient), pneumonia pneumococcal/pneumococcal sepsis/streptococcal bacteraemia (evolved to septic shock)/blood culture positive (all in 1 patient), pneumonia pneumococcal/septic shock (both in 1 patient), cellulitis (1 patient), and intervertebral discitis (1 patient).

Abbreviations: AE, adverse event; HLGT, High Level Group Terms; n, number of patients with at least one event; SOC, System Organ Classes

Source: Novartis Data on File. 2024 (Summary of Clinical Safety in C3 glomerulopathy; v1.0 Table 2-8 and Table 2-9).¹²⁵

2.11 Ongoing studies

As detailed in Section 2.5.2, the long-term clinical efficacy and safety of iptacopan in C3G are being examined in the open-label extension study (NCT03955445), which is ongoing and expected to complete in 2033.³⁵ The APPEAR-C3G study (NCT04817618) is ongoing for the adolescent C3G cohort (aged 12 to below 18 years of age), with an expected completion date in 2026,³² and anticipated to subsequently inform a regulatory submission for an extension of the licensed indication.

2.12 Interpretation of clinical effectiveness and safety evidence

Trial design and generalisability to UK clinical practice

APPEAR-C3G is the first placebo-controlled clinical trial in C3G. The double-blind, placebo-controlled methodology during the randomised treatment period represents a major strength of the study, in a disease area where prospective and controlled evidence for current SoC is lacking.^{25-27, 33, 104} Iptacopan was directly compared with placebo whilst also allowing use of concomitant medications such as ACEis/ARBs, MMF, CS or SGLT2i (at a stable dose), reflecting the current UK SoC for C3G.^{27, 33} APPEAR-C3G therefore provides methodologically robust, relevant and meaningful comparative data for the clinical effectiveness and safety of iptacopan for the treatment of adults with C3G.^{27, 33}

The sample size of APPEAR-C3G (N=74) was reflective of the ultra-rare nature of C3G, which may have contributed to some imbalances in baseline characteristics between the randomised treatment groups.³³ Patients in the iptacopan arm had notably higher proteinuria at baseline and exhibited a steeper pre-trial eGFR decline than the placebo arm, suggesting a more severe disease phenotype.^{27, 33} Comparisons between groups may therefore underestimate the efficacy of iptacopan.²⁷

The placebo-controlled period of APPEAR-C3G was limited to 6 months for ethical reasons, with patients randomised to placebo subsequently switching to open-label iptacopan for the remainder of the 12-month study.³³ Proteinuria, a well-recognised risk factor for progression to kidney failure,^{3, 17, 25, 64, 67, 69-72} decreased rapidly with iptacopan treatment, with a statistically significant reduction in UPCR demonstrated in comparison with placebo at 6 months.³³ Iptacopan arm data at 6 months further suggested a stabilisation in eGFR (CfB of +1.30 mL/min/1.73m²; 95% CI: -2.14, 4.73), whereas placebo arm data was suggestive of further decline (CfB -0.86; 95% CI: -4.36, 2.64);³³ clinicians suggested that the 6-month duration of the double-blind treatment period may have been too short to show a statistically significant effect in the comparison between groups.²⁷ Longer-term data from the extension study – whilst lacking a placebo control arm – suggest stabilisation of kidney function with continued iptacopan treatment;¹²⁴ in comparison, with current SoC approximately 50% of patients progress to kidney failure within 10 years of diagnosis.^{3, 16, 18, 19}

UK nephrologists and complement specialists consulted in a Novartis UK advisory board in November 2024 (N=10) considered data from APPEAR-C3G generalisable to UK clinical practice.²⁷ The clinicians confirmed that clinical characteristics at baseline and historical eGFR decline were reflective of the UK C3G population and patients who advisors considered would be expected to benefit from iptacopan treatment in clinical practice.²⁷ Most advisors agreed that it was reasonable to focus on patients with elevated proteinuria (UPCR ≥ 1 g/g or ≥ 113 mg/mmol) despite use of a maximally tolerated dose of an ACEi or ARB, consistent with the APPEAR-C3G inclusion criteria.²⁷ The proportion of patients in APPEAR-C3G on background medication of Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

MMF and/or CS (44.6%) was considered in line with current UK experience, reflecting the absence of targeted treatment options; however, clinicians emphasised the importance of being able to use iptacopan ahead of MMF/CS in clinical practice, given the limited evidence for efficacy of these treatments in C3G.²⁵⁻²⁷

Advisors further highlighted that generalisability of the trial data to UK clinical practice was also supported by the UK being well-represented within the iptacopan C3G studies. In APPEAR-C3G, 12.2% of patients (9/74) were from the UK and the majority of patients were from study sites in Europe. Similarly, 29.6% of patients (8/27) enrolled in the Phase 2 study were from the UK.²⁷

Given the high rate of post-transplant recurrence of C3G, exclusion of transplanted patients from the APPEAR-C3G study is a limitation of the evidence base. However, data on the efficacy and safety of iptacopan in patients with post-transplant recurrent C3G are available from the iptacopan Phase 2 study.³⁷ In addition, given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients.^{27, 40} Due to the small sample size in the Phase 2 post-transplant cohort, the lack of a comparator arm in the single-arm trial, and no suitable evidence identified for an ITC, a robust economic analysis in post-transplant patients was not considered feasible. However, the approach to model only a native kidney population aligns with that taken in previous NICE appraisals in various other chronic kidney diseases, without this leading to exclusion of transplanted patients from the NICE recommendation (see Appendix E, Table 12).

Clinical effectiveness of iptacopan

APPEAR-C3G met its primary efficacy endpoint, with a statistically significant and clinically meaningful reduction in 24h UPCR by 35.1% (95% CI: 13.8%, 51.1%; $p=0.0014$) compared with placebo on top of optimised background therapy at the end of the 6-month double-blind period.³³ The benefit of iptacopan on proteinuria was further substantiated by a decrease in the proportion of patients with nephrotic-range proteinuria (UPCR ≥ 3 g/g), as well as an increase in the proportion of patients achieving UPCR <1 g/g.³³ Improvements in UPCR were sustained over the open-label period of APPEAR-C3G and in the extension study with data up to 2 years.^{33, 124} UK experts at the advisory board considered the UPCR reduction with iptacopan as clinically meaningful and strong evidence of its efficacy in C3G; achieving a UPCR <1 g/g, as observed for some patients in the iptacopan arm of the trial (baseline: 0%; Month 6: 10.5%; Month 12: 23.7%),³³ was seen as particularly encouraging, although advisors highlighted that any proteinuria reduction is beneficial.²⁷

Proteinuria results were supported by the effect of iptacopan on eGFR, as key measure of kidney function. The CfB to 6 months in eGFR (secondary endpoint), as measured by the adjusted mean difference of iptacopan versus placebo, was 2.16 mL/min/1.73m² (95% CI: -2.75, 7.06; multiplicity-adjusted 1-sided p-value: 0.3241).³³ While statistical significance was not met, clinical experts suggested that this was as expected after only 6 months of follow up.²⁷ Given the ultra-rare nature of C3G, the trial population was small and therefore less powered to detect smaller changes in eGFR that would be expected after a short follow-up period.²⁷ eGFR slope analyses based on longer follow-up were considered more robust and meaningful by advisors.²⁷ Collection of historical data from APPEAR-C3G participants enabled a comprehensive comparison with patients' longer-term pre-trial eGFR trajectory, providing further context to the change in eGFR decline following initiation of iptacopan treatment. Prior to initiation of iptacopan treatment, patients included in APPEAR-C3G had a rapid decline in eGFR of -7.22 mL/min/1.73 m²/year (95% CI: -10.10, -4.35; estimated based on up to 2.5 years of pre-iptacopan data).¹²⁴ With a Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

mean baseline eGFR of 94.1 mL/min/1.73 m² and no change in treatment, this would be expected to result in kidney failure within approximately 11 years, consistent with observed C3G real-world data including from the UK (RaDaR).^{3, 16-19, 27} Treatment with iptacopan led to stabilisation of the eGFR decline, with the on-iptacopan slope estimated as -0.29 mL/min/1.73m²/year (95% CI: -3.88, 3.31; analysis including extension study data with up to 2 years iptacopan treatment duration). This equated to a change in annual eGFR slope of 6.94 mL/min/1.73m² (95% CI: 3.48, 10.39; p=0.0001) compared with pre-iptacopan treatment, suggesting that iptacopan is able to slow the progression of C3G in a meaningful way.^{27, 124} An additional analysis pooling data from APPEAR-C3G and the native kidney cohort of the Phase 2 study, with up to 4.7 years of iptacopan treatment duration, further confirmed this conclusion (see Section 2.8.1).

UK clinicians agreed that both UPCR and eGFR were clinically relevant outcome measures.²⁷ Increasing evidence supports the link between reduction in proteinuria and both preservation of eGFR and reduced risk of kidney failure.^{72, 134} This includes evidence from UK patients with C3G in RaDaR, where reductions in UPCR and a decrease in eGFR decline were both associated with a lower risk of kidney failure,³ suggesting that the efficacy of iptacopan demonstrated in APPEAR-C3G can lead to improved clinical outcomes for people with C3G. By reducing the risk of kidney failure, iptacopan is expected to reduce the need for dialysis and transplant, which is anticipated to translate into positive impacts on the quality of life of people living with C3G,^{7, 93} as well as alleviate NHS capacity constraints for dialysis and transplants.¹⁰⁶

In addition to being the first treatment with placebo-controlled trial evidence in C3G, iptacopan is further differentiated from currently used treatments by its targeted mode of action as a proximal complement inhibitor.²⁷ While current SoC does not address the underlying pathophysiology of C3G and predominantly constitutes supportive care, iptacopan demonstrated rapid and sustained effects on multiple biomarkers for complement alternative pathway dysregulation.³³ In conjunction with benefits seen in clinical outcomes, this further supports iptacopan as a disease-modifying treatment of C3G.^{27, 33}

Safety of iptacopan

The safety of oral iptacopan 200 mg b.i.d. in patients with C3G has been well characterised in the iptacopan C3G clinical trial programme, with overall 189.8 patient-years of exposure.¹²⁵ Iptacopan was well tolerated with the majority of AEs being mild or moderate in severity, and no evidence of increased risk of TEAEs with longer exposure. Observed SAEs suspected to be related to iptacopan were consistent with the known risks of complement inhibitors, which may predispose patients to serious infections with encapsulated bacteria.¹²⁵ Vaccination prior to treatment start is required as part of the iptacopan label, to reduce the risk of serious infections,^{30, 49} and experience and guidance in managing the risks of complement inhibitors are available from the use of iptacopan and other complement inhibitors in PNH as well as the use of C5 inhibitors in atypical haemolytic uraemic syndrome (aHUS).¹³³

3 Cost effectiveness

Modelling approach and structure

- A *de novo* economic analysis was developed for this submission to evaluate the cost-effectiveness of iptacopan in addition to SoC versus SoC alone for adults with C3G
- The model is a Markov cohort model with health states for CKD stages 1, 2, 3a, 3b, 4, 5 (pre-KRT), dialysis, post-transplant, and death, with a cycle length of 3 months and a lifetime horizon
- Progression through CKD stages over time is modelled based on eGFR slope data
- The analysis was conducted in accordance with the NICE reference case³⁹

Model inputs

- Patient baseline characteristics in the model were based on data from APPEAR-C3G³³
- Transition probabilities for progression through CKD stages were estimated for SoC and iptacopan from eGFR slope analyses using pre-iptacopan and on-iptacopan data, respectively, from patients enrolled in APPEAR-C3G including longer-term follow-up data from the extension study¹²⁴
- Model inputs relating to KRT (dialysis, transplant, graft failure) were primarily informed by RaDaR data from UK patients with C3G¹⁷
- Utility values for CKD stages 1–4 were mapped from EQ-5D-5L collected in APPEAR-C3G,³³ derived with a mixed effects linear regression model. Utility values for CKD stage 5 (pre-KRT) and KRT were informed by literature,^{135, 136} as used in previous NICE appraisals
- Costs included treatment acquisition, disease monitoring, and transplant/dialysis costs, as well as AE management and vaccination/antibiotic costs for patients treated with iptacopan
- Iptacopan treatment discontinuation and AE rates were sourced from the broad safety set of the pooled iptacopan trials in C3G, leveraging all available data¹²⁵

Cost-effectiveness results

- At the PAS price, the results of the deterministic base-case economic analysis show iptacopan + SoC is associated with 1.74 incremental quality-adjusted life years (QALYs) at an incremental cost of [REDACTED] versus SoC alone. The resulting incremental cost-effectiveness ratio (ICER) versus SoC is [REDACTED] per QALY gained
- Results from the probabilistic sensitivity analysis (PSA) were consistent with the deterministic base-case results. The probabilistic base-case ICER stabilised from approximately ~150 iterations

- [REDACTED]

3.1 Published cost-effectiveness studies

To identify published cost-effectiveness studies for interventions in C3G, an SLR was conducted in September 2020, and subsequently updated in October 2024. Despite keeping the scope of the SLR broad and searching a wide range of sources, no studies meeting the inclusion criteria were identified. Full details of the methodology of the economic evaluations SLR, including the search strategy and the study selection process, are presented in Appendix E.

Given the lack of published cost-effectiveness studies in C3G, an additional targeted literature review (TLR) was undertaken of NICE technology appraisals in chronic kidney diseases with final guidance published in the last 10 years, in order to support economic model development and inform potential sources for input values. The TLR methodology is described in Appendix E. The TLR identified 13 NICE appraisals meeting the inclusion criteria, with key features of the economic analyses summarised in Table 31. The majority of appraisals identified deployed a Markov model, while two appraisals used patient-level simulations (TA599 and TA358)^{137, 138} and one used a microsimulation (TA942).¹³⁹ Cycle length ranged from four weeks to one year.¹³⁷⁻¹⁴⁰ Health states varied, with some appraisals defining health states primarily in terms of CKD stage^{137-139, 141-145} while others focused on other features of the respective disease.^{140, 145-149} Appraisals which modelled CKD progression commonly utilised eGFR data from the clinical trial,^{138, 139, 141, 143, 144, 146} while some appraisals relied on literature or clinical expert opinion.^{137, 142, 145}

Table 31: Key features of published NICE technology appraisals in chronic kidney diseases

TA (year)	Population	Intervention (I); Comparator (C)	Model type	Health states	Cycle length	Modelling of CKD progression
TA942 (2023) ¹³⁹	Adults with CKD	- I: Empagliflozin in addition to individually optimised SoC - C: Individually optimised SoC	Microsimulation	19 health states: 18 KDIGO health states (defined by eGFR and UACR) - Death	1 year	eGFR and UACR of each patient are individually tracked in the model. Annual treatment-specific transition probabilities between KDIGO health states were derived from mean annual eGFR slopes and UACR changes observed over time in the pivotal trial (eGFR slope and UACR change estimated individually for each KDIGO state)
TA937 (2023) ¹⁴¹	Adults with primary IgAN at risk of rapid disease progression with a UPCR ≥ 1.5 g/g	- I: Targeted-release (TR) budesonide in addition to SoC - C: SoC	Markov model	9 health states: - CKD stages 1, 2, 3a, 3b, 4, 5 (pre-KRT) - Dialysis - Transplant - Death	1 month	Transition probabilities between CKD stages 1–4 estimated from pivotal trial eGFR data, using logistic regression. Risk of transition from CKD stage 4 to 5 in SoC arm informed by RaDaR registry data; treatment effect of TR budesonide applied as HR based on relationship of 1-year eGFR slope and clinical outcome as estimated in a published meta-analysis
TA890 (2023) ¹⁴⁰	Adults with CKD-associated pruritus who are on haemodialysis	- I: Difelikefalin in addition to established clinical management - C: Established clinical management	Markov model	7 health states: 5 itch severity health states (none, mild, moderate, severe, and very severe) - Transplant - Death	4 weeks	N/A
TA882 (2023) ¹⁴²	Adults with active lupus nephritis	- I: Voclosporin in combination with MMF and low-dose CS - C: MMF + CS - C: Cyclophosphamide + CS - C: Azathioprine + CS	Markov model	9 health states: - Complete response (CR) with CKD stages 1-3a - Partial response (PR) with CKD 1-3a - Active disease (AD) with CKD 1-3a	6 months	Transition probabilities for progression from CKD stages 1-3a to 3b-4 and from 3b-4 to 5 were informed by clinical expert input

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TA (year)	Population	Intervention (I); Comparator (C)	Model type	Health states	Cycle length	Modelling of CKD progression
		- C: Rituximab - C: Tacrolimus + MMF/CS		- CR with CKD 3b-4 - PR with CKD 3b-4 - AD with CKD 3b-4 - CKD stage 5, dialysis - CKD stage 5, after kidney transplant - Death		
TA877 (2023) ¹⁴³	Adults with CKD and type-2 diabetes mellitus	- I: Finerenone in addition to SoC background therapy - C: SoC background therapy	Markov model	13 health states: 4 health states for CKD progression (CKD stage 1/2, 3, 4, 5 without renal replacement therapy; defined by eGFR) 2 states for ESRD (dialysis, post-transplant) 4 corresponding CKD progression and 2 corresponding ESRD health states for patients after experiencing a first CV event in the model - Death	4 months	Transition probabilities between CKD stages (based on changes in eGFR) derived from trial IPD, based on the observed numbers of patients in each health state over 4-month intervals. Assumption that transition probabilities are constant over model time horizon
TA825 (2022) ¹⁴⁶	Adults with anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV)	- I: Avacopan in combination with cyclophosphamide or rituximab - C: Rituximab or cyclophosphamide in combination with CS	Markov model	9 health states: - Active disease 3 remission health states 3 relapse health states - ESRD (dialysis or transplant) - Death	28 days	Baseline probability of ESRD from published literature was adjusted by a hazard ratio per eGFR unit decrease (using eGFR change from baseline for avacopan and comparator from pivotal trial, and HR for ESRD per mL/min change in eGFR from baseline from literature)
TA809 (2022) ¹⁴⁷	Adults with CKD awaiting a kidney transplant from a	- I: Imlifidase - C: Dialysis	Markov model	3 health states: - On dialysis - Functioning graft - Death	6 months	N/A

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TA (year)	Population	Intervention (I); Comparator (C)	Model type	Health states	Cycle length	Modelling of CKD progression
	donor, who are highly sensitised					
TA807 (2022) ¹⁴⁸	Adults with symptomatic anaemia associated with CKD who are not dialysis-dependent at the time of treatment initiation	- I: Roxadustat - C: Erythropoiesis stimulating agents (ESA; modelled as a class)	Markov model	9 health states: 8 health states for anaemia based on different ranges of haemoglobin levels - Death (Dialysis considered separately for cost and healthcare resource use)	3 months	Time to dialysis was estimated using parametric survival regression models on trial data. No treatment effect was included in time to dialysis (treatment targets anaemia, not CKD)
TA775 (2022) ¹⁴⁴	Adults with CKD	- I: Dapagliflozin in addition to optimised SoC - C: Optimised SoC alone (established clinical management)	Markov model	9 health states: - CKD stages 1, 2, 3a, 3b, 4, 5 (pre-KRT) - Dialysis - Transplant - Death	1 month	Treatment-specific transition probabilities between CKD stages and progression from CKD stages to dialysis or kidney transplant were derived from the pivotal trial, using monthly transition count data to generate a transition probability matrix based on observed eGFR trajectories
TA623 (2020) ¹⁴⁵	Adults with CKD stage 3-4 with hyperkalaemia (HK)	- I: Patiromer - C: No patiromer	Markov model	6 health states: - CKD stage 3-4 with mild HK - Moderate to severe HK - CV event - Post-CV event - CKD progression (ESRD) - Death	1 month	Monthly probability of progression from CKD stage 3-4 to ESRD derived from literature
TA599 (2019) ¹³⁷	Adults with HK and an underlying condition of CKD or heart failure (HF)	- I: Sodium zirconium cyclosilicate - C: Standard care	Patient-level simulation	8 health states: 4 health states for HF by NYHA class 4 health states for CKD stages 3a, 3b, 4, 5 pre-KRT + Absorbing states: patients leave the model due to commencing KRT; all-cause	4 weeks	Progression of CKD is modelled via the decline of eGFR on a continuous scale, based on literature. Progression through CKD stages is tracked until the onset of ESRD and the initiation of KRT

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TA (year)	Population	Intervention (I); Comparator (C)	Model type	Health states	Cycle length	Modelling of CKD progression
				mortality; HF mortality; CKD mortality		
TA481 (MTA) (2017) ¹⁴⁹	Adult kidney transplant recipients	Overall, 16 regimens modelled in MTA, including basiliximab, rabbit anti-human thymocyte/ antithymocyte (immune)globulin (ATG), tacrolimus, MMF, mycophenolate sodium, sirolimus, everolimus, belatacept, in combination with CS and ciclosporin and/or azathioprine	Semi-Markov model	3 health states: • Functioning graft • Graft loss (dialysis-dependent) • Death	3 months	N/A
TA358 (2015) ¹³⁸	Adults with autosomal dominant polycystic kidney disease (ADPKD)	• I: Tolvaptan • C: No active treatment (no drug cost)	Patient-level simulation	2 model parts with overall 10 health states: • 1) ADPKD progression module: CKD stage 1, 2, 3, 4 • 2) ESRD module: CKD prior to ESRD treatment; conservative care; HD; PD; transplant; Death	1 year	Disease progression in the comparator arm (natural history) was modelled based on changes in total kidney volume (TKV) and eGFR, as predicted from disease progression equations. For the intervention arm, treatment effect was applied based on annual eGFR slope (absolute change in eGFR per year), as observed in the trial

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody-associated vasculitis; AD, active disease; ADPKD, autosomal dominant polycystic kidney disease; ATG, rabbit anti-human thymocyte/ antithymocyte (immune)globulin; C, comparator; CKD, chronic kidney disease; CR, complete response; CS, corticosteroids; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis stimulating agents; ESRD, end-stage renal disease; HF, heart failure; HD, haemodialysis; HK, hyperkalaemia; HR, hazard ratio; I, intervention; IgAN, immunoglobulin A nephropathy; IPD, individual patient data; KDIGO, Kidney Disease: Improving Global Outcomes; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; MTA, multiple technology appraisal; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; PD, peritoneal dialysis; PR, partial response; RaDaR, National Registry of Rare Kidney Diseases; SoC, standard of care; TA, technology appraisal; TKV, total kidney volume; TR, targeted release; UACR, urine albumin-to-creatinine ratio

Sources: Empagliflozin for treating chronic kidney disease (TA942);¹³⁹ Targeted-release budesonide for treating primary IgA nephropathy (TA937);¹⁴¹ Difelikefalin for treating pruritus in people having haemodialysis (TA890);¹⁴⁰ Voclosporin with mycophenolate mofetil for treating lupus nephritis. (TA882);¹⁴² Finerenone for treating chronic kidney disease in type 2 diabetes (TA877);¹⁴³ Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis (TA825);¹⁴⁶ Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease (TA809);¹⁴⁷ Roxadustat for treating symptomatic anaemia in chronic kidney disease (TA807);¹⁴⁸ Dapagliflozin for treating chronic kidney disease (TA775);¹⁴⁴ Sodium zirconium cyclosilicate for treating hyperkalaemia (TA599);¹³⁷ Patiromer for treating hyperkalaemia (TA623);¹⁴⁵ Immunosuppressive therapy for kidney transplant in adults (TA481);¹⁴⁹ Tolvaptan for treating autosomal dominant polycystic kidney disease (TA358).¹³⁸

Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

3.2 Economic analysis

Given the absence of published economic evaluations and previous NICE appraisals in C3G, a *de novo* economic analysis relevant to the decision problem for this evaluation was developed to evaluate the cost-effectiveness of iptacopan in addition to SoC versus SoC alone. The economic model was developed with input from UK clinical and health economic experts,^{27, 40} and built in Microsoft Excel®.

3.2.1 Patient population

The population addressed in this submission and in the economic analysis is adults with C3G, consistent with the population detailed in the NICE final scope. In line with the design of the clinical trials, the model considers patients with continued risk of disease progression on a maximally tolerated licensed dose of an ACEi or ARB. The baseline characteristics for individuals entering the model are summarised in Section 3.3.1.

Economic modelling is based on iptacopan trial data from patients with native kidney C3G as included in the APPEAR-C3G study. For patients with post-transplant recurrence, the sample size of the respective cohort of the Phase 2 trial (N=11) did not permit a robust economic analysis. However, given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients.^{27, 40} Furthermore, the approach to model only a native kidney population aligns with that taken in previous NICE appraisals in other chronic kidney diseases, with the NICE recommendations for these treatments not excluding transplanted patients even where transplanted patients were excluded from the clinical trials. Further details are provided in Appendix E, Table 12.

3.2.2 Model structure

A *de novo* health-state transition model was developed, using a Markov approach, modelling the progression of CKD to kidney failure and KRT.

The model has a lifetime time horizon (up to age 100 years), in line with the NICE reference case.³⁹ A cycle length of 3 months was considered to provide sufficient detail to capture the impact on costs and QALYs as patients progressed through the model.

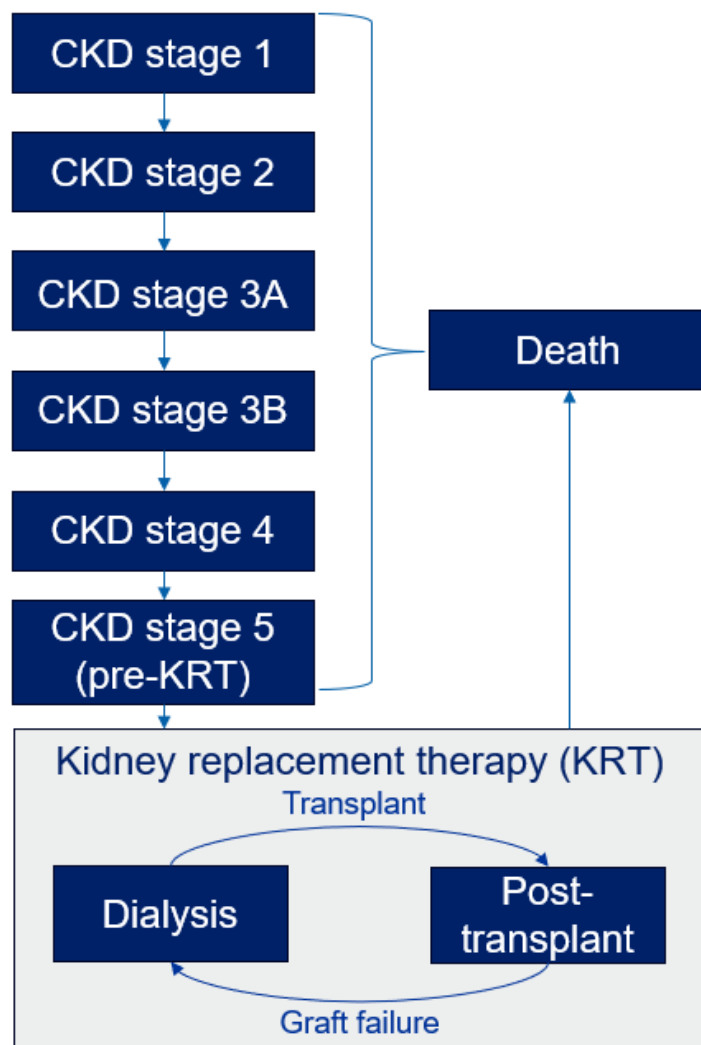
The model contains nine mutually exclusive health states – six health states representing CKD stages 1–5, two KRT health states (dialysis and post-transplant), and death as an absorbing state. The model structure is illustrated in Figure 27. At the start of the model, patients with C3G are distributed across CKD stages 1–4, and over the time horizon sequentially progress through subsequent (worse) CKD stages based on their decline in eGFR. To limit technical complexity, the model does not allow for backwards transitions to less severe CKD stages, however, the impact of this simplification is considered limited since sustained improvements to less severe CKD stages are not expected to occur in clinical practice with current SoC.

Once a patient's eGFR reaches the KRT threshold (defined as eGFR ≤ 7.6 mL/min/1.73 m² in the base case; see Section 3.3.2.2), they either receive a pre-emptive transplant and are assigned to the 'Post-transplant' health state or initiate chronic dialysis and are assigned to the 'Dialysis' health state. Patients on dialysis have a per-cycle probability of receiving a transplant in each cycle, while transplanted patients have a per-cycle probability of experiencing graft failure in each cycle, requiring a return to dialysis. The model allows for multiple transplants with multiple

instances of graft failure over the time horizon, reflecting a common cycle of transplant and dialysis as experienced by patients with C3G.^{17, 27, 104}

Patients can transition directly to the death state from any other health state.

Figure 27: Model schematic



CKD stage 1: eGFR ≥ 90 mL/min/1.73 m²; CKD stage 2: eGFR 60–89 mL/min/1.73 m²; CKD stage 3a: 45–59 mL/min/1.73 m²; CKD stage 3b: 30–44 mL/min/1.73 m²; CKD stage 4: 15–29 mL/min/1.73 m²; CKD stage 5 (pre-KRT): < 15 mL/min/1.73 m².

Abbreviations: CKD: chronic kidney disease. KRT: kidney replacement therapy.

The model health states are consistent with two previous recent appraisals in IgAN (TA937)¹⁴¹ and CKD (TA775)¹⁴⁴ and were confirmed by UK clinicians to be relevant and key determinants of quality of life and costs in C3G.²⁷ Given that CKD stages are defined by eGFR, use of eGFR trial data was considered the most direct approach to modelling disease progression,⁴⁰ which is in alignment with the approach taken in several previous appraisals in other chronic kidney diseases (Table 31). While the primary endpoint of APPEAR-C3G was reduction in proteinuria (UPCR), use of this endpoint for economic modelling would have required relying on a surrogacy relationship with clinical outcomes, which is not yet robustly established in quantitative terms for complement inhibitors as a new, disease-modifying class of treatments for C3G.⁴⁰ Therefore, use of eGFR was preferred for economic modelling, with the approach described in further detail in Section 3.3.2.

3.2.2.1 Features of the economic analysis

Key features of the base-case economic analysis and their justifications are summarised in Table 32.

Table 32: Key features of the base-case economic analysis

Factor	Current evaluation	
	Chosen values	Justification
Patient population	Adults with C3G	In line with the final scope and expected licence
Model structure	Markov model	- In line with most previous appraisals in other chronic kidney diseases (Table 31) - The included health states are considered relevant to capture key aspects of the condition²⁷
Time horizon	Lifetime horizon (72.1 years in the base case, up to age 100)	In line with the NICE reference case³⁹ and reflects lifelong nature of C3G
Cycle length	3 months - A half-cycle correction was implemented using the life table method, where the time in each cycle is estimated by taking the average of the number of people at the start and end of the cycle	- A 3-month cycle length was considered to provide sufficient detail to capture the impact on costs and QALYs as patients progressed through the model - Aligned with prior appraisals in other chronic kidney diseases (Table 31) which included cycle lengths ranging from 4 weeks–1 year
Perspective	NHS and PSS	In line with the NICE reference case³⁹
Discounting per year of costs and utilities	Annual rate of 3.5% for costs and outcomes	In line with the NICE reference case³⁹
Treatment waning effect?	- Treatment effect was assumed as constant over the model time horizon, while patients remained on treatment - Following discontinuation of iptacopan, no residual treatment effect was assumed	- Based on clinical advice, the pharmacological effect of iptacopan is not expected to change over time and therefore, the treatment effect is not expected to wane.⁴⁰ If applicable, modelled discontinuations were assumed to capture any decline in effectiveness⁴⁰ (Section 3.3.3) - Assumption of no residual effect after discontinuation based on clinical opinion⁴⁰
Source of clinical efficacy and safety	- Efficacy: APPEAR-C3G, including long-term extension study data - Safety: broad safety set including data from APPEAR-C3G, Phase 2	APPEAR-C3G is the pivotal clinical trial for iptacopan in C3G and therefore the primary source of data, with the extension study providing longer-term follow-up data for efficacy inputs^{33, 124}

Factor	Current evaluation	
	Chosen values	Justification
	and long-term extension studies	Safety inputs were informed by the broad safety set, including all available iptacopan trial data in C3G¹²⁵
Source of utilities	- CKD stages 1–4: APPEAR-C3G - CKD stage 5 (pre-KRT), dialysis, post-transplant, AE disutility: literature	- EQ-5D-5L collected in APPEAR-C3G allowed the estimation of health state utility values for CKD stages 1–4 based on data from the population of interest (adults with C3G)³³ - For health states following kidney failure, no data were available from APPEAR-C3G. In the absence of suitable published utility values for people with C3G, values in people with CKD were sourced from the literature, as used in previous NICE appraisals (Section 3.4.3) - Selection of all utility values was based on input from clinical and health economic experts⁴⁰
Source of costs	- eMIT,¹⁵⁰ NHS reference costs,¹⁵¹ PSSRU unit costs,¹⁰⁸ BNF⁵¹ - Relevant literature - Clinical expert opinion for disease monitoring frequency and tests conducted²⁷	- NHS cost sources were used in line with the NICE reference case³⁹ - Where costs were not available from established sources within the NHS, costs were derived from relevant literature - As published health state costs for CKD were not considered plausible,⁴⁰ C3G-specific monitoring costs were estimated based on clinical expert opinion (survey responses from 9 UK clinicians)²⁷ (Section 3.5.2)

Abbreviations: AE, adverse event; BNF, British National Formulary; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; eMIT, electronic marketing information tool; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year.

3.2.3 Intervention technology and comparators

The intervention is modelled as iptacopan + SoC, in line with the APPEAR-C3G trial³³ and the proposed positioning of iptacopan in the C3G treatment pathway (Figure 5). Iptacopan is modelled as 200 mg oral capsules which are taken twice daily.

In line with the final scope of this appraisal, the comparator is SoC alone, which may include ACEi, ARB, CS, MMF, and SGLT2i (see Section 1.3.5), reflecting the current SoC for people with C3G in the UK as confirmed by UK clinical experts.^{26, 27} The exact treatment regimens modelled as components of the SoC basket, along with the proportion of patients receiving each component, are detailed in Section 3.5.1.

3.3 Clinical parameters and variables

3.3.1 Patient characteristics

In the base case, patient characteristics were taken from the APPEAR-C3G population, in line with the source of eGFR slope data used for modelling disease progression (Section 3.3.2). A scenario analysis using eGFR slope data pooled across trials included patient characteristics from the pooled trial population. The impact of utilising baseline characteristics from a UK real-world cohort with C3G was explored in an additional scenario analysis, using patient characteristics from RaDaR.¹⁷ RaDaR cohort characteristics at time of diagnosis rather than at latest follow-up were used based on clinical experts' advice, since characteristics at latest follow-up represent a prevalent population whose C3G has progressed in the absence of effective treatments; clinicians advised that these would be less reflective of future expected clinical practice where iptacopan is anticipated to be initiated earlier in the disease course.²⁷

Table 33. Baseline patient characteristics utilised in the economic model

Parameter	APPEAR-C3G (base case)	Pooled trial data (scenario)	RaDaR (scenario)
Baseline age, years	27.9	27.6	28.9
Proportion female	36.5%	36.7%	46.1%
Mean eGFR ^a , mL/min/1.73m ²	92.8	88.4	78.2
CKD stage 1	58.1%	52.2%	38.4%
CKD stage 2	23.0%	23.3%	27.3%
CKD stage 3a	6.8%	7.8%	10.1%
CKD stage 3b	9.5%	13.3%	14.1%
CKD stage 4	2.7%	3.3%	10.1%

^aCalculated for modelled population based on CKD stage at baseline, assuming all patients are in the midpoint of the stage. Please note for CKD stage 1, the mean eGFR at baseline of APPEAR-C3G patients in CKD stage 1 is used, since CKD stage 1 does not have an upper bound for calculation of a midpoint.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RaDaR, National Registry of Rare Kidney Diseases.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Tables 10-3 and 10-4);³³ Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 glomerulopathy; v1.0 Table 1-3.1);¹²⁴ Novartis Data on File. 2024 (C3G RaDaR Priority Analysis, Interim Enrichment Report).¹⁷

3.3.2 Transition probabilities

3.3.2.1 Modelling disease progression using eGFR slope

Disease progression was modelled based on eGFR data from the iptacopan clinical trials in C3G. Whilst several previous appraisals had used trial eGFR data to generate transition probabilities from observed transitions between CKD stages (Table 31), this was not deemed feasible in this case due to the small sample size and the low number of patients in more advanced CKD stages at baseline (Table 33). Therefore, transition through CKD stages was modelled based on eGFR slope.

eGFR slope options for the SoC arm were discussed as potential model inputs with 10 UK clinicians in an advisory board conducted by Novartis in November 2024 (Table 34).²⁷ Advisors were aligned that the eGFR slope generated from the 6-month placebo arm data of APPEAR-C3G (Option 1) was inconsistent with published literature and their clinical experience with current SoC in C3G.^{27, 33} While published analyses based on real-world data, including RaDaR,³ Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

estimate a median time from diagnosis to kidney failure of approximately 10 years, extrapolation of the placebo arm data of APPEAR-C3G would overestimate kidney survival by a factor of about 2.3–2.6 (time to kidney failure [eGFR <15 mL/min/1.73m²] with annual eGFR decline of –3.079: 25.7 years, if calculated from baseline eGFR of 94.1 mL/min/1.73m² without consideration of mortality; model-predicted: 22.8 years).³³ This was not considered plausible by advisors, and they explained that 6 months of data from 36 patients were likely insufficient to robustly estimate eGFR slope.²⁷ On the other hand, time to kidney failure predictions for the SoC arm of approximately 10–11 years, generated from eGFR slopes based on 2.5 years of pre-iptacopan data from patients enrolling in iptacopan clinical trials in C3G (Table 34, Options 2 and 3), were considered to be in line with registry data and clinical experience.^{27, 40, 124}

Since predictions based on placebo arm data lacked clinical validity,^{27, 40} pre-iptacopan data were therefore used to model disease progression in the SoC arm and compared with on-iptacopan data. Based on advice from clinical and health economics experts, eGFR slopes from the APPEAR-C3G population were selected as base case (N=74; Table 34, Option 2).^{33, 40} eGFR slopes from a pooled analysis of the APPEAR-C3G and Phase 2 (native kidney cohort) populations (N=90; Option 3) were explored in a scenario analysis.¹²⁴ An additional scenario analysis was conducted using data from the 6-month double-blind period of APPEAR-C3G only (Option 1);³³ however, results should be interpreted with caution due to the lack of clinical validity of the predictions for SoC.^{27, 40}

Table 34: eGFR slope inputs for the economic model

Option	Population	Analysis	Annual eGFR slope, mL/min/1.73 m ² /year (95% CI)			Use in economic model
			SoC	Iptacopan	Iptacopan treatment effect	
1	APPEAR-C3G	• SoC: placebo arm data from 6-month double-blind period (N=36) • Iptacopan: iptacopan arm data from 6-month double-blind period (N=38)	-3.079 (-10.131, 3.973)	-0.025 (-6.929, 6.878)	3.053 (-6.815, 12.922)	Scenario analysis
2	APPEAR-C3G	• SoC: pre-iptacopan data, up to 2.5 years (N=74) • Iptacopan: on-iptacopan data, up to 2 years treatment duration^a (N=74)	-7.224 (-10.101, -4.348)	-0.289 (-3.884, 3.305)	6.935 (3.481, 10.390)	Base case
3	Pooled population: APPEAR-C3G and Phase 2 native kidney cohort (Cohort A)	• SoC: pre-iptacopan data, up to 2.5 years (N=90) • Iptacopan: on-iptacopan data, up to 4.7 years treatment duration^a (N=90)	-8.317 (-10.891, -5.744)	-0.701 (-3.765, 2.363)	7.616 (4.616, 10.616)	Scenario analysis

Pre-iptacopan data includes historical values (up to 2 years prior to trial enrolment or since C3G diagnosis if less than 2 years), screening/run-in data and placebo arm data from the 6-month double-blind period of APPEAR-C3G. On-iptacopan data includes all data from initiation of iptacopan treatment, including data from patients originally randomised to the placebo arm of APPEAR-C3G after switching to open-label iptacopan at Day 180. ^aIncluding treatment in the open-label extension study.

Abbreviations: C3G, complement 3 glomerulopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; SoC, standard of care.

Sources: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 14.2-16.2.1);³³ Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 1 Tables 2-1.2 and 2-1.1).¹²⁴

The average change in eGFR in a 1-year period was represented by eGFR slope (rate of eGFR decline), for both SoC (based on the pre-iptacopan period) and iptacopan. The eGFR slopes for SoC and iptacopan, respectively, were used to model progression from one CKD stage to the next, generating transition probabilities. The time to move between states was defined as the time taken for eGFR to decline from the midpoint of the current CKD stage to the midpoint of the following stage. This approach assumes a uniform distribution of patients across a CKD stage and was used in the base case following validation with clinical and health economics experts.⁴⁰ The clinical expert noted, however, that the use of the midpoint would not be appropriate for transitions to KRT, as this would model that patients commence KRT only at an eGFR of 3.8 mL/min/1.73m² (midpoint between KRT threshold [7.6 mL/min/1.73m²] and 0).⁴⁰ Therefore, to better reflect UK clinical practice, transitions to KRT were modelled to take place at the KRT threshold instead (7.6 mL/min/1.73m²). A scenario analysis was conducted to test the impact of using the upper eGFR bound to calculate transition probabilities for all transitions (between CKD stages and to KRT).

The probability of progression in each 3-month cycle was calculated as per the following formula:

$$p_{i \rightarrow i+1} = 1 - \exp \left(\frac{\text{rate of eGFR decline}}{4 * (M_i - M_{i+1})} \right)$$

Where $p_{i \rightarrow i+1}$ is the probability of progressing from CKD stage i to CKD stage $i + 1$ and M_i is the eGFR value at the midpoint of stage i . Since CKD stage 1 is defined as eGFR ≥ 90 mL/min/1.73m² and thus has no upper bound, the mean eGFR value of patients in CKD stage 1 at baseline in APPEAR-C3G was used as the midpoint instead (116.9 mL/min/1.73m²).

While the rate of eGFR decline may vary over the course of disease, the sample size of the iptacopan trials in C3G did not permit estimation of CKD stage-dependent eGFR decline rates. As such, a simplifying assumption that speed of progression is independent of CKD stage and constant over the course of disease was applied.

Table 35 summarises the probability of progression from each stage in the base-case analysis. Equivalent tables for scenario analyses are presented in Appendix K.

Table 35: Per-cycle probability of progression (base case)

	CKD stage 1	CKD stage 2	CKD stage 3A	CKD stage 3B	CKD stage 4	CKD stage 5 (pre-KRT)	KRT	Source
eGFR corresponding to CKD stage (mL/min/1.73m²)	≥90	60–89	45–59	30–44	15–29	<15–>7.6	≤7.6	
SoC								
Rate of eGFR decline (mL/min/1.73m²/year)	–7.224						N/A (see Section 3.3.2.2)	APPEAR-C3G ^a
Time to next state (years)	5.80	3.11	2.08	2.08	1.55	0.52	N/A	Calculated
Rate of progression to next state (per year)	0.17	0.32	0.48	0.48	0.64	1.94	N/A	
Probability of progression to next state (per 3-month cycle)	4.22%	7.71%	11.34%	11.34%	14.86%	38.43%	N/A	
Iptacopan + SoC								
Rate of eGFR decline (mL/min/1.73m²/year)	–0.289						N/A (see Section 3.3.2.2)	APPEAR-C3G ^a
Time to next state (years)	144.86	77.85	51.90	51.90	38.84	12.89	N/A	Calculated
Rate of progression to next state (per year)	0.01	0.01	0.02	0.02	0.03	0.08	N/A	
Probability of progression to next state (per 3-month cycle)	0.17%	0.32%	0.48%	0.48%	0.64%	1.92%	N/A	

^aIncluding iptacopan data from the open-label extension study.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; N/A, not applicable; SoC, standard of care.

Source: Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Appendix 1 Table 2-1.2).¹²⁴

3.3.2.2 Modelling of kidney replacement therapy (KRT)

Once individuals reach kidney failure, they require KRT in the form of dialysis or a kidney transplant. In the economic model, patients were assumed to start KRT at an eGFR value of 7.6 mL/min/1.73 m². The NICE guideline for renal replacement therapy (NG107) recommends starting dialysis at an eGFR of around 5 to 7 mL/min/1.73 m² if the person has no symptoms, or earlier if symptoms require it.¹² The UK Renal Registry, which collects and reports data annually on approximately 70,000 people receiving KRT in the UK, reports that dialysis was on average started at an eGFR value of approximately 7 mL/min/1.73 m², while pre-emptive (without first receiving dialysis) transplants took place at an eGFR of approximately 10 mL/min/1.73 m².¹⁵³ This was in line with estimates from clinicians in the C3G advisory board.²⁷ For the economic model base case, the threshold to start KRT was set at 7.6 mL/min/1.73 m², derived as a weighted average of the above values, accounting for 18.4% of UK patients with C3G receiving a pre-emptive transplant as their first KRT modality, based on RaDaR data.¹⁷ This was confirmed to be a reasonable assumption by a UK clinical expert.⁴⁰ A scenario analysis set the KRT threshold value to 10 mL/min/1.73 m², representing the average eGFR value at receipt of a pre-emptive transplant.¹⁵³

In the base case, upon reaching an eGFR value of 7.6 mL/min/1.73 m², 18.4% of patients are modelled to receive a pre-emptive transplant (based on RaDaR data), while the remaining 81.6% of patients start dialysis.¹⁷ Given the young average age at kidney failure, UK clinicians advised that all patients with C3G would be expected to commence KRT, with no patients receiving conservative management instead.²⁷

Adelphi DSP survey data from the EU4 and the UK indicated that among 107 people with C3G in need of a transplant, 18 (16.8%) were considered ineligible to receive a transplant.¹⁵⁴ This was accounted for in the analysis, by patients ineligible for a transplant remaining in the dialysis health state until death. In addition, it was assumed that patients aged ≥80 years would not receive a transplant in the base case (in line with NICE TA942 in CKD);¹³⁹ the impact of setting no upper age limit was explored in a scenario analysis. For patients on dialysis who are eligible for a transplant, an 8.7% probability of receiving a transplant in each 3-month cycle was incorporated in the model, derived from a RaDaR analysis in patients with C3G estimating a median time from start of dialysis to receipt of transplant (excluding pre-emptive transplants) of 1.9 years.¹⁷

People that received a transplant are modelled to be at risk of graft failure. Using RaDaR data from patients with C3G indicating a median time to graft failure post-transplant of 6.5 years, a per cycle probability of graft failure of 2.6% was included in the model.¹⁷ Upon graft failure, patients return to the dialysis health state but are tracked separately from non-transplanted dialysis patients in the model, in order to allow for continued consideration of post-transplant immunosuppression costs (Section 3.5.2). Following graft failure, it was assumed that a proportion of patients were no longer eligible for transplantation; in the base case, this was assumed to be same as the proportion that were ineligible for a first transplant (16.8%). In the base case, this results in people in the SoC arm receiving on average 1.9 transplants over their lifetime, which a UK clinical expert considered plausible.⁴⁰ However, UK clinicians also provided feedback that the proportion of patients ineligible for a first transplant may be lower and the proportion ineligible for a subsequent transplant may be higher, given that with increasing age, they may develop more comorbidities and become more sensitised.^{27, 40} Therefore, a scenario analysis assumed that 6.8% were ineligible for a first and 26.8% for a subsequent transplant (reflecting base case value +/- 10%, respectively).

Input values relating to KRT utilised in the model base case are summarised in Table 36.

Table 36. KRT inputs in the model base case

KRT parameter	Input value	Source
eGFR threshold for starting KRT	7.6 mL/min/1.73 m ²	UK Renal Registry ¹⁵³
Patients ineligible for a kidney transplant	16.8%	Adelphi DSP survey data for patients with C3G ¹⁵⁴
Assumed maximum age for receipt of transplant	80 years	NICE TA942 ¹³⁹
Patients receiving a pre-emptive transplant as their first KRT modality	18.4%	RaDaR analysis in patients with C3G ¹⁷
Median time from start of dialysis to transplant (excluding patients receiving a pre-emptive transplant)	1.9 years (8.7% probability per 3-month cycle of receiving a transplant)	
Median time from transplant to graft failure	6.5 years (2.6% probability per 3-month cycle of having graft failure)	

Abbreviations: C3G, complement 3 glomerulopathy; DSP, Disease Specific Programme; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; RaDaR, National Registry of Rare Kidney Diseases. **Source:** UK Kidney Association. 2024 (UK Renal Registry 26th Annual Report).¹⁵³ Novartis Data on File. 2023 (Adelphi DSP Supplementary Data).¹⁵⁴ NICE. 2023 (Empagliflozin for treating chronic kidney disease [TA942]).¹³⁹ Novartis Data on File. 2024; (C3G RaDaR Priority Analysis, Interim Enrichment Report).¹⁷

3.3.3 Treatment discontinuation and subsequent therapy

3.3.3.1 Discontinuation prior to kidney failure

The iptacopan discontinuation rate among patients who have not reached kidney failure was based on all-cause treatment discontinuation of iptacopan in the pooled APPEAR-C3G, Phase 2 and extension studies (broad safety set).¹²⁵ Overall, there were 13 permanent discontinuations from iptacopan across the pooled cohort, in a total of 189.8 patient-years of exposure. Information on reasons for discontinuation is provided in Table 37. When deriving the discontinuation rate for use in the economic model, one discontinuation due to death was excluded from the calculation, to avoid double-counting of deaths in the model.⁴⁰ This resulted in a rate of discontinuation of 0.063 per year, with a per cycle probability of discontinuation of 1.57%.

SoC treatments were assumed not to be discontinued prior to kidney failure.

Table 37: Reason for iptacopan treatment discontinuation in pooled trials

Reason for treatment discontinuation, n (%)	Iptacopan (N=101)
Adverse event	3 (3.0)
Progressive disease	2 (2.0)
Physician decision	3 (3.0)
Subject decision	4 (4.0)
Death ^a	1 (1.0)
Total	13 (12.9)

^aNot considered in estimation of discontinuation rate for use in the economic model to avoid double-counting of deaths

Source: Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 1 Table 1–1.1.1).¹²⁴

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3.3.3.2 Discontinuation following kidney failure

Based on input received from UK clinicians,²⁷ the base case assumed that patients would discontinue iptacopan treatment at the point of commencing KRT. The same discontinuation assumption was applied for all components of the SoC basket except for ACEi/ARB, since UK clinicians were aligned that these would usually be continued while on KRT, due to their blood pressure-lowering effects.^{26, 27} A scenario analysis assumed that all treatments, except for ACEi/ARB, were discontinued once patients reached CKD stage 5 (eGFR <15 mL/min/1.73m²).

3.3.3.3 Subsequent therapy following iptacopan discontinuation

Within the model, patients that discontinue iptacopan subsequently receive SoC alone, with the eGFR slope of the SoC arm applied from the point of iptacopan discontinuation onwards. No residual treatment effect of iptacopan was modelled following discontinuation, based on clinical advice.⁴⁰

3.3.4 Adverse events

In the double-blind, placebo-controlled period of APPEAR-C3G, no single severe TEAE occurred in more than one patient in either the iptacopan or the placebo arm.³³

To ensure the impact of AEs associated with iptacopan which would be likely to affect QALYs and costs was still captured in the model, serious AEs (SAEs) suspected to be related to iptacopan were included. Data from the broad safety set (pooled trial populations) were used for maximum sample size and follow-up duration (N=101; 189.8 patient-years). Due to the absence of a placebo control arm following the 6-month double-blind period of APPEAR-C3G, only SAEs suspected to be related to iptacopan were included, rather than all SAEs.¹²⁵

In the pooled population, there were 4 patients who experienced overall 9 SAEs suspected to be related to iptacopan (Table 38). However, in 2 patients, several SAEs occurred concurrently and were linked to each other.^{40, 125} Therefore, based on clinical advice, the incidence of SAEs suspected to be related to iptacopan for use in the economic model was calculated based on overall 5 SAE episodes (Table 38).⁴⁰ In 189.8 patient years, this corresponded to a 0.66% probability of SAEs per 3-month model cycle. A scenario analysis tested the impact of assuming 9 SAEs in 189.8 patient years, corresponding to a 1.18% probability of SAEs per 3-month model cycle.

Almost all SAEs suspected to be related to iptacopan were infections with encapsulated bacteria (an AE of special interest for iptacopan; Section 2.10.6) leading to pneumonia or consequences thereof such as sepsis,^{40, 125} and considered accordingly in the economic analysis for AE disutilities (Section 3.4.4) and costs (Section 3.5.3).⁴⁰

Table 38. SAEs suspected to be related to iptacopan treatment (broad safety set; N=101)

Patients	Day of onset	SAE suspected to be related to iptacopan
Patient 1	████	Blood culture positive (for streptococcus pneumoniae)
Patient 1 ^a	████	Pneumonia pneumococcal
	████	Pneumococcal sepsis
	████	Streptococcal bacteraemia (evolved to septic shock)
Patient 2	████	Pneumonia pneumococcal
	████	Septic shock
	████	Acute respiratory distress syndrome

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Patients	Day of onset	SAE suspected to be related to iptacopan
Patient 3	████	Norovirus infection
Patient 4	████	Pneumocystis jirovecii pneumonia

^aSubsequent SAE episode

Abbreviations: SAE, serious adverse event.

Source: Novartis Data on File. 2024 (Summary of Clinical Safety in C3 Glomerulopathy, Table 2-5).¹²⁵

3.3.5 Mortality

As described in Section 1.3.4, the impact of C3G on life expectancy is not well reported. Therefore, data to capture excess mortality associated with CKD in the model were sourced from a broader population. Hazard ratios (HRs) as a function of CKD stage were combined with data on mortality for the general population (as a function of age and sex) to estimate the absolute mortality risk in the model, using 2021–2023 general population life tables for England and Wales.¹⁵⁵

A study by Wong et al. 2024 reported mortality ratios, standardised to the general population of England and Wales, for patients in RaDaR with and without kidney failure, respectively (Table 39).¹⁴ While not C3G-specific, this recent analysis was based on a total of 27,285 people from the UK with rare kidney diseases, including 1,089 people with either C3G or MPGN,¹⁴ and recommended by clinical experts for use in the economic model.²⁷

A scenario analysis used HRs from a US longitudinal study including 1,120,295 adults who had ≥ 1 outpatient measure of creatinine (Go et al. 2004) for pre-transplant mortality,⁸⁴ and a study of people with Type 1 diabetes and a functioning kidney transplant in the Finnish Kidney Transplant Registry (N=2,543; Ortiz et al. 2019) for post-transplant mortality.¹⁵⁶

Table 39. Mortality hazard ratios used in the economic model

CKD stage	Wong et al. 2024 ¹⁴ (base case)	Go et al. 2004 ⁸⁴ (scenario)
	SMR	HR
CKD stage 1	1.32 (95% CI: 1.13, 1.51) (patients without kidney failure)	1.0 (reference group)
CKD stage 2		1.2 (95% CI: 1.1, 1.2)
CKD stage 3a		1.8 (95% CI: 1.7, 1.9)
CKD stage 3b		3.2 (95% CI: 3.1, 3.4)
CKD stage 4	3.99 (95% CI: 3.55, 4.42) (patients with kidney failure) ^a	5.9 (95% CI: 5.4, 6.5)
CKD stage 5, pre-KRT		3.9 ^b
Dialysis		
Post-transplant (functioning kidney)		

^aDefined as patients receiving KRT or with an eGFR ≤ 15 mL/min/1.73m² before 1 year after recruitment date.¹⁴

^bHR for post-transplant patients informed by Ortiz et al. 2019.¹⁵⁶

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; KRT, kidney replacement therapy; SMR, standardised mortality ratio.

Sources: Wong et al. 2024;¹⁴ Go et al. 2004;⁸⁴ Ortiz et al. 2019.¹⁵⁶

3.3.6 Cardiovascular events

Since no data could be identified on the risk of cardiovascular (CV) events in patients with C3G and clinicians considered that literature from CKD more broadly may overestimate the incidence of CV events,^{27, 40} CV events were included in a scenario analysis only. All associated parameters are presented in Appendix K.

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3.4 Measurement and valuation of health effects

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

EQ-5D-5L data were collected in APPEAR-C3G at baseline, Day 14, 30, 90, 180, 210, 270, and 360.³³ Overall, 74 patients contributed 484 EQ-5D measurements which could be used to generate utility values. Since the majority of people participating in APPEAR-C3G were in an early stage of disease, no EQ-5D data were available from the trial for CKD stage 5 (pre-KRT) and for patients receiving KRT; utility values for these health states were therefore sourced from the literature (see Section 3.4.3). The EQ-5D-5L data collected in APPEAR-C3G were mapped to EQ-5D-3L (see Section 3.4.2). Table 40 presents the mapped health state utility values. The mean utility value for CKD stage 1 was deemed implausible as it was lower than the values for CKD stages 2 and 3.

Table 40: Mapped utility values by health state in APPEAR-C3G

Health state	Frequency	Mean	SD
CKD stage 1	286	0.883	0.149
CKD stage 2	108	0.926	0.091
CKD stage 3	74	0.900	0.129
CKD stage 4	16	0.825	0.140

Abbreviations: CKD, chronic kidney disease; SD, standard deviation.

In addition to generating mean utility values based on observed data, a mixed effects linear model for repeated measures was fit to all utility values obtained at baseline and all other visits where patients completed the EQ-5D questionnaire. The model included covariates for CKD stage (with CKD stage 1 as reference), age, sex, and utility at baseline. Consistent with the mean values by CKD stage, the model found that utility values were higher in CKD stage 2 versus stage 1, though this was not statistically significant.

An alternative model specification pooled CKD stages 1 and 2, which resulted in a plausible pattern of utility values by CKD stage. The approach of combining these stages has been used previously in the published literature, for example in Jesky et al. 2016, a UK study which assessed EQ-5D-3L among 745 people with CKD of any aetiology.¹³⁵ The regression models are presented in Table 41. In alignment with feedback from UK clinical and health economic experts, utility values generated with the regression model pooling CKD stages 1 and 2 were used for the base case analysis.⁴⁰ A scenario analysis used utility values from the literature, as published in Jesky et al. 2016 (see Section 3.4.3).¹³⁵

Table 41: Utility regression models based on APPEAR-C3G data

	Model 1 – By individual CKD stage			Model 2 – Pooled CKD stages 1 and 2		
	Coefficient	SE	95% CI	Coefficient	SE	95% CI
Health state (reference in Model 1: CKD stage 1; reference in Model 2: pooled CKD stages 1+2)						
CKD stage 2	0.013	0.014	-0.013, 0.040	-	-	-
CKD stage 3	-0.035	0.021	-0.077, 0.007	-0.042	0.021	-0.082, -0.002
CKD stage 4	-0.050	0.034	-0.116, 0.016	-0.057	0.033	-0.121, 0.008
Baseline utility	0.735	0.064	0.610, 0.859	0.733	0.064	0.608, 0.859
Age	0.001	0.001	-0.001, 0.002	0.001	0.001	-0.001, 0.002

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	Model 1 – By individual CKD stage			Model 2 – Pooled CKD stages 1 and 2		
	Coefficient	SE	95% CI	Coefficient	SE	95% CI
Proportion of males	0.037	0.017	0.003, 0.070	0.039	0.017	0.005, 0.072
Constant	0.855	0.024	0.808, 0.902	0.853	0.024	0.806, 0.900

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

3.4.2 Mapping

EQ-5D-5L data collected in APPEAR-C3G were mapped to EQ-5D-3L using the Hernández-Alava mapping algorithm recommended by NICE.¹⁵⁷

3.4.3 Health-related quality-of-life studies

To identify published health-related quality of life (HRQoL) studies in C3G, an SLR was conducted in January 2021, and subsequently updated in November 2024. Two multinational studies were identified which provided utility values for patients with C3G based on EQ-5D-5L. One of these studies was a randomised controlled clinical trial which reported utility values at baseline and at 26 weeks for the intervention and comparator arms, but did not provide values for the model health states.¹⁵⁸ The other study reported utility values based on EQ-5D-5L collected from patients with C3G (n=100) as part of the Adelphi DSP and mapped using a US tariff.⁸ While this study provided utilities for CKD stages 1–4/5, these were not considered clinically plausible,⁴⁰ since CKD stage 1 patients had the worst HRQoL after patients with CKD stage 4/5 (utility values for CKD stage 1: 0.67; 2: 0.77; 3a: 0.80; 3b: 0.70; 4/5: 0.58).⁸ Therefore, utility values from both studies were deemed unsuitable for use in the model. Full details of the methodology and results of the HRQoL SLR are presented in Appendix F.

While utility values for CKD stages 1–4 could be informed by APPEAR-C3G trial data (Section 3.4.1), utility values from the literature were still required for CKD stage 5 (pre-KRT), dialysis, and transplant. Therefore, in addition to the SLR for C3G-specific utilities which did not identify any suitable values, NICE technology appraisals in chronic kidney diseases with final guidance published in the last 10 years were reviewed in a TLR. The sources for utility values which informed the NICE Committee's decision making in these appraisals are summarised in Table 42, with further details provided in Appendix F.

Out of the 13 previous NICE appraisals in chronic kidney diseases identified in the TLR, only two appraisals (TA877 finerenone for CKD in type 2 diabetes;¹⁴³ TA775 dapagliflozin for CKD)¹⁴⁴ utilised utility values generated from trial data for CKD stages 1–5 (pre-KRT); all other utility values used in previous appraisals were informed by literature. A publication from Jesky et al. 2016¹³⁵ was a commonly used source for utility values for CKD stages 1–5 (pre-KRT). Utility values for dialysis and transplant were most commonly informed by a publication from Lee et al. 2005¹³⁶ (7 appraisals), with a few appraisals using utilities from Liem et al. 2008¹⁵⁹ (2 appraisals) or Li et al. 2017¹⁶⁰ (2 appraisals; Table 42). Further details on these studies are provided in Section 3.4.4.

Table 42: Health state utility sources in previous NICE technology appraisals in chronic kidney diseases

TA (year)	CKD stages 1–4	CKD stage 5, pre-KRT	Dialysis	Transplant
TA942 (2023) ¹³⁹	Jesky et al. 2016 ¹³⁵	Jesky et al. 2016 ¹³⁵	Liem et al. 2008 ¹⁵⁹	Lee et al. 2005 ¹³⁶
TA937 (2023) ¹⁴¹	Jesky et al. 2016 ¹³⁵	Jesky et al. 2016 ¹³⁵	Lee et al. 2005 ¹³⁶	Lee et al. 2005 ¹³⁶
TA890 (2023) ¹⁴⁰	N/A	N/A	N/A	Lee et al. 2005 ¹³⁶
TA882 (2023) ¹⁴²	N/A	N/A	Cooper et al. 2020 ¹⁰⁵	Li et al. 2017 ¹⁶⁰
TA877 (2023) ¹⁴³	Trial data	Trial data	NG28 ¹⁶¹	NG28 ¹⁶¹
TA825 (2022) ¹⁴⁶	N/A	N/A	Lee et al. 2005 ¹³⁶	Lee et al. 2005 ¹³⁶
TA809 (2022) ¹⁴⁷	N/A	N/A	Li et al. 2017 ¹⁶⁰	Li et al. 2017 ¹⁶⁰
TA807 (2022) ¹⁴⁸	Ara & Brazier 2011 ¹⁶²	Ara & Brazier 2011 ¹⁶²	Lee et al. 2005 ¹³⁶	N/A
TA775 (2022) ¹⁴⁴	Trial data	Trial data	Lee et al. 2005 ¹³⁶	Lee et al. 2005 ¹³⁶
TA623 (2020) ¹⁴⁵	Jesky et al. 2016 ¹³⁵	N/A	Jesky et al. 2016 ¹³⁵	Jesky et al. 2016 ¹³⁵
TA599 (2019) ¹³⁷	Eriksson et al. 2016 ¹⁶³	Eriksson et al. 2016 ¹⁶³	N/A	N/A
TA481 (MTA) (2017) ¹⁴⁹	N/A	N/A	Liem et al. 2008 ¹⁵⁹	Liem et al. 2008 ¹⁵⁹
TA358 (2015) ¹³⁸	Gorodetskaya et al. 2005 ¹⁶⁴	Lee et al. 2005 ¹³⁶	Lee et al. 2005 ¹³⁶	Lee et al. 2005 ¹³⁶

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy, MTA, multiple technology appraisal; N/A, not applicable; NG, NICE Guideline; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Sources: Cooper et al. 2020;¹⁰⁵ Li et al. 2017;¹⁶⁰ NICE 2022. (NG28);¹⁶¹ Ara and Brazier. 2011;¹⁶² Eriksson et al. 2016;¹⁶³ Gorodetskaya et al. 2005;¹⁶⁴ Liem et al. 2008;¹⁵⁹ Lee et al. 2005;¹³⁶ Jesky et al. 2016;¹³⁵ Empagliflozin for treating chronic kidney disease (TA942);¹³⁹ Targeted-release budesonide for treating primary IgA nephropathy (TA937);¹⁴¹ Difelikefalin for treating pruritus in people having haemodialysis (TA890);¹⁴⁰ Voclosporin with mycophenolate mofetil for treating lupus nephritis. (TA882);¹⁴² Finerenone for treating chronic kidney disease in type 2 diabetes (TA877);¹⁴³ Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis (TA825);¹⁴⁶ Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease (TA809);¹⁴⁷ Roxadustat for treating symptomatic anaemia in chronic kidney disease (TA807);¹⁴⁸ Dapagliflozin for treating chronic kidney disease (TA775);¹⁴⁴ Sodium zirconium cyclosilicate for treating hyperkalaemia (TA599);¹³⁷ Patiromer for treating hyperkalaemia (TA623);¹⁴⁵ Immunosuppressive therapy for kidney transplant in adults (TA481);¹⁴⁹ Tolvaptan for treating autosomal dominant polycystic kidney disease (TA358).¹³⁸

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

3.4.4.1 Health state utility values

Utility values generated from APPEAR-C3G trial data or identified in the TLR were reviewed with UK clinical and health economic experts with regards to their suitability for use in the economic model.⁴⁰ For CKD stages 1–4, utility values based on EQ-5D-5L collected in patients with C3G in the APPEAR-C3G trial (baseline mean age 27.9 years) were preferred for the base-case

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analysis, utilising values estimated with the regression model pooling CKD stages 1 and 2.⁴⁰ Jesky et al. 2016,¹³⁵ a UK study which collected EQ-5D-3L data from 745 patients with CKD of any aetiology and a median age of 64 years, was considered appropriate to inform the utility value for CKD stage 5 (pre-KRT), for which no data were available from APPEAR-C3G.⁴⁰ A scenario analysis explored the impact of using utility values from Jesky et al. 2016 for CKD stages 1–5 (pre-KRT).¹³⁵

To inform dialysis and post-transplant utilities in the economic model, experts considered the values published by Lee et al. 2005,¹³⁶ which were used in 7 previous NICE appraisals, as most appropriate.⁴⁰ Lee et al. 2005, a UK study, estimated utility values for different KRT modalities from EQ-5D-3L collected in 416 patients (mean age 55.5 years in women, 58.2 years in men),¹³⁶ using a UK tariff;¹⁶⁵ utility values for haemodialysis (HD), peritoneal dialysis (PD), and post-transplant were reported as 0.44, 0.53, and 0.71, respectively.¹³⁶ For the dialysis utility in the economic model, a weighted average was calculated according to the proportion of patients receiving each type of dialysis, sourced from a RaDaR analysis in patients with C3G (HD: 85.3%; PD: 14.7% [APD: 11.8%, CAPD: 2.9%])¹⁷.

Utility values from Liem et al. 2008¹⁵⁹ and Li et al. 2017¹⁶⁰ were also discussed with clinical and health economics experts but not considered suitable for use in the model.⁴⁰ The methodology of Liem et al. 2008¹⁵⁹ was considered to introduce uncertainty, since it is a meta-analysis of EQ-5D-based utility values reported across multiple international studies which did not consistently provide information on the value sets used; experts therefore preferred using Lee et al. 2005, given that it was a UK study.⁴⁰ In addition, the small difference in the utility values of HD (0.56) and PD (0.58) reported by Liem et al. 2008¹⁵⁹ may underestimate the negative HRQoL impact of 3x weekly in-centre HD compared to at-home PD.⁴⁰

Utility values from Li et al. 2017¹⁶⁰ were not considered suitable for use in the economic model by the experts for several reasons.⁴⁰ The publication reported a utility value for people on the transplant waiting list (0.77), rather than people on dialysis, and the clinical expert highlighted that people on the transplant waiting list tend to be healthier than people on long-term dialysis.⁴⁰ This value was therefore not seen as representative of the HRQoL of people receiving chronic dialysis. Furthermore, the study used the preliminary value set for England to generate utility values from EQ-5D-5L,¹⁶⁶ which NICE advises against utilising.¹⁶⁷ Therefore, based on expert advice,⁴⁰ utility values from Li et al. 2017 were not used in the analysis.

All health state utility values utilised in the base case and scenario analysis are summarised in Table 43.

Age adjustments were applied in the model to adjust for differences between the source population's age for literature-based utility values and the baseline age of the modelled population, as well as capture declining HRQoL as the population ages over the model time horizon. Reported utility values were divided by the corresponding general population utility from Hernández-Alava et al. 2022 (age- and sex-matched on the source publication study cohort)¹⁵⁷ to derive a multiplier. This multiplier was then applied in the model to the general population utility of the modelled population, with the general population utility decreasing over time as the population ages.¹⁵⁷ Where utility values were above the relevant general population value, the multiplier used in the model was capped at 1. The approach for age adjustments was validated with a UK health economist,⁴⁰ and age adjustments are shown in Table 43.

Table 43: Health state utility values used in the economic model

Health state		Reported utility value for study population (95% CI)	Source	Age- and sex-matched general population utility for study population	Utility multiplier applied to general population utility for model population	Modelled utility at baseline
Base case						
CKD stage 1		0.91	APPEAR-C3G	0.92	0.99	0.91
CKD stage 2		0.91			0.99	0.91
CKD stage 3a		0.86			0.94	0.86
CKD stage 3b		0.86			0.94	0.86
CKD stage 4		0.85			0.92	0.85
CKD stage 5 (pre-KRT)		0.73 (0.62–1.00)	Jesky et al. 2016 ¹³⁵	0.83	0.88	0.81
Dialysis ^a	HD	0.44 (SD: 0.32)	Lee et al. 2005 ¹³⁶	0.83	0.53 ^a	0.49 ^a
	PD	0.53 (SD: 0.34)		0.84	0.63 ^a	0.58 ^a
Post-transplant		0.71 (SD: 0.27)	Lee et al. 2005 ¹³⁶	0.86	0.82	0.76
Scenario analysis						
CKD stage 1		0.85 (0.70–1.00)	Jesky et al. 2016 ¹³⁵	0.83	1.00	0.92
CKD stage 2		0.85 (0.70–1.00)			1.00	0.92
CKD stage 3a		0.80 (0.69–1.00)			0.97	0.89
CKD stage 3b		0.80 (0.69–1.00)			0.97	0.89
CKD stage 4		0.74 (0.62–0.85)			0.90	0.82
CKD stage 5 (pre-KRT)		0.73 (0.62–1.00)			0.88	0.81

^aThe modelled utility for dialysis was based on a weighted average according to the proportion of patients receiving each type of dialysis, sourced from RaDaR (PD: 14.7%, HD: 85.3%).¹⁷

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HD, haemodialysis; KRT, kidney replacement therapy, PD, peritoneal dialysis; RaDaR, National Registry of Rare Kidney Diseases; SD, standard deviation.

Sources: Jesky et al. 2016;¹³⁵ Lee et al; 2005.¹³⁶

3.4.4.2 AE disutilities

As described in Section 3.3.4, SAEs suspected to be related to iptacopan were included in the model. Given that most of these were infections, a disutility associated with infections was included in the model. The disutility was taken from a study by Oppong et al. 2013,¹⁶⁸ which was identified through a published SLR on the impact of acute pneumococcal disease on health state utility values.¹⁶⁹ Oppong et al. 2013 collected EQ-5D-3L from patients in England with cough and lower respiratory tract infections in a longitudinal manner and generated utility values using the UK tariff.¹⁶⁸ The difference in utility between acute presentation (baseline) and recovery (week 4) was reported as 0.156, which was used in the model as disutility for infections.¹⁶⁸ The duration for the disutility was assumed as 32.1 days, in line with the mean duration of SAEs suspected to be related to iptacopan in the broad safety set trial data.¹²⁵

3.4.4.3 Cardiovascular event disutilities

As noted above, CV events were modelled as part of a scenario analysis, with the associated disutilities presented in Appendix K.

3.5 Cost and healthcare resource use identification, measurement and valuation

The base-case economic analysis considers the following cost categories:

- Drug acquisition costs
- Healthcare resource use costs (including disease monitoring, transplant, and dialysis costs)
- Vaccination and antibiotic costs
- AE management costs
- End of life costs

Where costs were not available from established sources within the NHS, such as the National Schedule of NHS Costs 2023/2024¹⁵¹ or PSSRU Unit Costs of Health and Social Care 2023,¹⁰⁸ costs were derived from relevant literature. All relevant costs were inflated to the 2022/2023 fiscal year using the NHSCII Pay and Price Index, pending the release of an updated PSSRU unit cost manual.¹⁰⁸

Cost and healthcare resource use (HCRU) studies in C3G were searched for in an SLR conducted in February 2021 and subsequently updated in October 2024. The cost and HCRU SLR identified 6 publications presenting data on HCRU in C3G, however no relevant evidence for use in this submission was identified within these publications. Further details are provided in Appendix G.

Since no relevant information on HCRU in C3G was identified in the SLR, an additional TLR was undertaken of NICE technology appraisals in chronic kidney diseases with final guidance published in the last 10 years. The sources for health state costs which informed the NICE Committee's decision making in these appraisals are summarised in Table 44, with further details provided in Appendix G. The costs in these appraisals were derived from a number of sources, including NHS reference costs, NICE guidelines and a number of publications in CKD.

Full details of the costs included in the base-case economic analysis and how they are applied within the model are presented in the following sections.

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Table 44: Health state cost sources in previous NICE technology appraisals in chronic kidney diseases

TA (year)	CKD stages 1–4	CKD stage 5 (pre-KRT)	Dialysis	Transplant (one-off)	Post-transplant (long-term)
TA942 (2023) ¹³⁹	Pollock et al. 2022	Pollock et al. 2022	CAPD, APD: NHS reference cost; HD: TA877	NHS reference cost	TA775
TA937 (2023) ¹⁴¹	Kent et al. 2015 (secondary care); clinical opinion for primary care cost	Kent et al. 2015 (secondary care); clinical opinion for primary care cost	NHS reference cost; Liu et al. 2015 for HD transport cost; clinical opinion for nephrologist visits, blood tests and hospitalisations	NHS reference cost	Clinical opinion; TA481
TA890 (2023) ¹⁴⁰	N/A	N/A	NHS reference cost	NHS reference cost	NHS Blood and Transplant 2009
TA882 (2023) ¹⁴²	N/A	N/A	NICE NG107 2018	Kerr et al. 2012; NHS reference cost	Kerr et al. 2012b
TA877 (2023) ¹⁴³	NICE TA358	NICE TA358	NICE CG GID-NG10118 2021 (draft)	NICE CG GID-NG10118 2021 (draft)	NICE CG GID-NG10118 2021 (draft)
TA825 (2022) ¹⁴⁶	N/A	N/A	Kent et al. 2015	Kent et al. 2015	Kent et al. 2015
TA809 (2022) ¹⁴⁷	N/A	N/A	NHS reference cost; NHS drug tariff; Liu et al. 2015 for HD transport cost	NHS reference cost; BNF	NHS reference cost; NHS drug tariff; eMIT
TA807 (2022) ¹⁴⁸	N/A	N/A	NHS reference cost	N/A	N/A
TA775 (2022) ¹⁴⁴	Kent et al. 2015	Kent et al. 2015	NICE NG107	NHS reference cost	NHS Blood and Transplant 2009
TA623 (2020) ¹⁴⁵	Kerr et al. 2012	N/A	Kerr et al. 2012 (including transport cost)	Kerr et al. 2012	Kerr et al. 2012
TA599 (2019) ¹³⁷	NICE CG182 2015	NICE CG182 2015	N/A	N/A	N/A
TA481 (MTA) (2017) ¹⁴⁹	N/A	N/A	NHS reference cost	NHS reference cost	N/A

TA (year)	CKD stages 1–4	CKD stage 5 (pre-KRT)	Dialysis	Transplant (one-off)	Post-transplant (long-term)
TA358 (2015) ¹³⁸	Clinical opinion; NICE CG182	NICE CG182	NICE CG182; NHS reference cost; Baboolal et al. 2008; NICE CG125	NICE CG182; NHS reference cost; NHS Blood and Transplant (FOI request)	NICE CG182; Kerr et al. 2012

Abbreviations: APD, Automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; FOI, freedom of information; HD, haemodialysis; KRT, kidney replacement therapy; MTA, multiple technology appraisal; N/A, not applicable; NHS, National Health Service; PD, peritoneal dialysis; TA, technology appraisal

Sources: Baboolal et al. 2008;⁷⁶ Kent et al. 2015;¹⁷⁰ Kerr et al. 2012a;¹⁰⁷ Kerr. 2012b;⁴⁷ NHS Blood and Transplant. 2009;¹⁷¹ NICE (CG182). 2014;¹⁷² Pollock et al. 2022;¹⁷³ Empagliflozin for treating chronic kidney disease (TA942);¹³⁹ Targeted-release budesonide for treating primary IgA nephropathy (TA937);¹⁴¹ Difelikefalin for treating pruritus in people having haemodialysis (TA890);¹⁴⁰ Voclosporin with mycophenolate mofetil for treating lupus nephritis. (TA882);¹⁴² Finerenone for treating chronic kidney disease in type 2 diabetes (TA877);¹⁴³ Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis (TA825);¹⁴⁶ Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease (TA809);¹⁴⁷ Roxadustat for treating symptomatic anaemia in chronic kidney disease (TA807);¹⁴⁸ Dapagliflozin for treating chronic kidney disease (TA775);¹⁴⁴ Sodium zirconium cyclosilicate for treating hyperkalaemia (TA599);¹³⁷ Patiromer for treating hyperkalaemia (TA623);¹⁴⁵ Immunosuppressive therapy for kidney transplant in adults (TA481);¹⁴⁹ Tolvaptan for treating autosomal dominant polycystic kidney disease (TA358).¹³⁸

3.5.1 Intervention and comparator costs and resource use

Patients receiving iptacopan in the economic model incur costs of iptacopan 200 mg b.i.d. in addition to costs of background SoC therapies. Patients in the comparator arm incur costs associated with the background use of SoC only. Iptacopan and all SoC therapies are administered orally, incurring no administration costs.

The acquisition cost of iptacopan is presented in Table 45. The cost of iptacopan was set to £[REDACTED] per 28-day pack [REDACTED].

Table 45: Acquisition costs for iptacopan

Treatment	Dosing schedule	List price per pack	PAS price per pack	Unit size (mg)	Units per pack	Cost per day (PAS price)	Cost per year ^a (PAS price)
Iptacopan	200 mg b.i.d.	£26,500.00	[REDACTED]	200	56	[REDACTED]	[REDACTED]

Calculation based on 365.25 days per year

Abbreviations: b.i.d., twice daily; PAS, patient access scheme

As discussed in Section 1.3.5, SoC for patients with C3G can include ACEis/ARBs, MMF, CS, and SGLT2is. In the base case, the proportion of patients receiving each component of SoC was sourced from participant characteristics at baseline in APPEAR-C3G, and was assumed equal in the iptacopan and comparator arms.³³ While the proportion of patients in APPEAR-C3G on ACEi/ARB and CS and/or MMF was considered broadly reflective of UK clinical practice, clinical experts advised that the use of SGLT2i had become more common compared with the 5.4% of patients receiving SGLT2i as part of their background medication in the APPEAR-C3G study.²⁷ Therefore, a scenario analysis assumed the proportion of patients on SGLT2i as 50% (of note, this only impacts costs and not outcomes in the model).

Drug costs for SoC were taken from the 2023/2024 electronic market information tool (eMIT),¹⁵⁰ except the cost of dapagliflozin which was sourced from the BNF.⁵¹ The specific ACEi/ARBs included in the calculation reflect the most used treatments of each class in the UK cohort of an international cross-sectional study (Adelphi DSP);¹⁵⁴ for the other treatments, the cheapest medication of each class was selected. The acquisition costs associated with SoC are presented in Table 46.

Patients ceased to accrue treatment acquisition costs following discontinuation, with details described in Section 3.3.3.

Table 46: Acquisition costs for SoC

Treatment	Class	Dose per day (mg)	Price per pack	Source	Unit size (mg)	Units per pack	Proportion of patients	Weighted cost per day	Weighted cost per year
Ramipril	ACEi	10	£0.39	eMIT	10	28	47.3%	£0.01	£2.41
Losartan	ARB	50	£0.39	eMIT	50	28	52.7%	£0.01	£2.69
Dapagliflozin	SGLT2i	10	£36.59	BNF	10	28	5.4%	£0.07	£25.80
MMF	MMF	1,500	£6.45	eMIT	500	50	36.5%	£0.14	£51.57
Prednisolone	CS	7.5	£0.80	eMIT	2.5	30	32.4%	£0.03	£9.47
SoC (weighted cost)								£0.25	£91.95

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNF, British National Formulary; CS, corticosteroid; eMIT, electronic market information tool; MMF, mycophenolate mofetil; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Sources: BNF 2024;⁵¹ eMIT 2024;¹⁵⁰ Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data).³³

3.5.2 Health-state unit costs and resource use

Disease monitoring costs and healthcare resource use

Since no relevant literature could be identified, the outpatient resource use by patients with C3G was informed by a survey of UK clinicians participating in a Novartis advisory board conducted in November 2024.²⁷ Advisors were asked to provide information on the average number of routine monitoring visits per year for adult patients with C3G by CKD stage, as well as information regarding which tests they routinely conduct during monitoring visits, based on their current clinical practice. Overall 9 of the 10 advisory board participants completed the survey, with several advisors highlighting that monitoring frequency would also depend on a patient's level of proteinuria, rather than CKD stage alone.²⁷ The mean number of visits by CKD stage (Table 47) was calculated across all responses received and considered reasonable by a clinical expert.⁴⁰

At each monitoring visit, a range of monitoring tests was costed, based on input received in above-mentioned survey and subsequent discussion during the advisory board.²⁷ These are presented in Table 48 including unit costs and the per visit testing frequency. Unit costs were sourced from the NHS reference costs or PSSRU unit costs.^{108, 151}

A scenario analysis based disease monitoring frequency on the NICE guideline Chronic kidney disease: assessment and management (NG203), which provides recommendations on the minimum monitoring frequency for CKD (Table 47).¹¹

Table 47: Disease monitoring resource use

Resource use	Annual frequency of monitoring visits	
C3G clinical expert input from advisory board survey (base case)		
Nephrologist monitoring visits per year	CKD stage 1	2
	CKD stage 2	2
	CKD stage 3a	3
	CKD stage 3b	4
	CKD stage 4	5
	CKD stage 5 (pre-KRT) ^a	5
	Dialysis	3
	Post-transplant (long-term routine monitoring)	4
NICE CKD guideline (NG203) minimum monitoring frequency (scenario analysis)		
Nephrologist monitoring visits per year ^b	CKD stage 1	1
	CKD stage 2	1
	CKD stage 3a	2
	CKD stage 3b	2
	CKD stage 4	3
	CKD stage 5 ^c	4

^aAssumed equal to CKD stage 4 (health state was not included in advisory board survey); ^bMinimum frequency of monitoring visits for ACR category A3 was assumed, given the high levels of proteinuria in patients with C3G being treated with current SoC; ^cAssumed to also apply to patients on dialysis and post-transplant.

Abbreviations: ACR, albumin to creatinine ratio; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; KRT, kidney replacement therapy; NICE, National Institute for Health and Care Excellence; SoC, standard of care.

Sources: Novartis Data on File. 2024 (Advisory Board Report);²⁷ NICE (NG203). 2021.¹¹

Table 48: Per visit disease monitoring tests and unit costs

Resource	Unit cost	Frequency per visit	Unit cost source
Nephrologist visit	£206.69	1	NHS reference costs; Consultant led non-admitted face-to-face attendance, follow-up, WF01A, Renal Medicine Service, Outpatient care
eGFR test	£1.53	1	NHS reference costs; Directly Accessed Pathology Service, Currency code: PATH04 Clinical biochemistry, Service Code 999
Blood pressure check	£5.67	1	Assumed as 10 minutes of nurse time. PSSRU 2023; Hospital-based nurse, Band 4, unit cost per working hour
UPCR or UACR test ^a	£1.53	1	NHS reference costs; Directly Accessed Pathology Service, Currency code: PATH04 Clinical biochemistry, Service Code 999
Complement biomarker tests	£2.98	0.5 ^b	NHS reference costs; Directly Accessed Pathology Service, Currency code: PATH05 Haematology, Service Code 999
Full blood count	£2.98	1	NHS reference costs; Directly Accessed Pathology Service, Currency code: PATH05 Haematology, Service Code 999
Liver function tests	£1.53	1	NHS reference costs; Directly Accessed Pathology Service, Currency code: PATH04 Clinical biochemistry, Service Code 999

^aClinicians advised that either UPCR or UACR would be tested at every visit; ^bAssumed to be conducted at every 2nd visit, based on clinical expert advice that these would be conducted less frequently²⁷

Abbreviations: eGFR, estimated glomerular filtration rate; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio.

Sources: NHS National Cost Collection 2023/2024;¹⁵¹ Novartis Data on File. 2024 (Advisory Board Report);²⁷ PSSRU 2023.¹⁰⁸

Several previous NICE appraisals (TA937,¹⁴¹ TA775)¹⁴⁴ utilised a publication from Kent et al. 2015 to inform healthcare resource use.¹⁷⁰ Kent et al. 2015 estimated annual hospital costs, including hospital admissions and outpatient/day-case attendances, as part of a randomised trial in 7,246 people (mean age 63 years) with impaired kidney function in Europe, North America, and Australasia.¹⁷⁰ The study was considered as a potential alternative to modelling health state costs based on advisory board survey inputs. However, while Kent et al. 2015 included both in-patient and out-patient hospital care, the estimated costs (inflated to 2022/23 prices; Table 49) were too low to cover the costs of routine monitoring visits as advised specifically for patients with C3G by UK clinicians (Table 47 and Table 48), from CKD stage 3a onwards (for example, CKD stage 3a: 3 nephrologist visits at £206.69 each = £620.07, compared with £555.48 based on Kent et al.). Therefore, a UK clinician advised that it was preferable to utilise the advisory board survey inputs for the model base case.⁴⁰ The impact of using CKD stage costs based on Kent et al. 2015 was explored in a scenario analysis; in this analysis, disease monitoring resource use was set to zero, to prevent double counting of costs.

Table 49: Annual CKD hospital care costs based on Kent et al. 2015

Health state	Mean annual hospital care costs in the absence of diabetes and cardiovascular complications (inflated to 2022/2023 prices)	Source
CKD stage 1–3b	£555.48	Kent et al. 2015 ¹⁷⁰
CKD stage 4	£541.70	

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Health state	Mean annual hospital care costs in the absence of diabetes and cardiovascular complications (inflated to 2022/2023 prices)	Source
CKD stage 5, pre-KRT	£723.64	

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy

Sources: Kent et al. 2015;¹⁷⁰ PSSRU 2023.¹⁰⁸

Transplant and dialysis costs

Dialysis and kidney transplant costs are presented in Table 50. The one-time cost of kidney transplant was based on 2023/2024 NHS reference costs, following a calculation approach used in previous NICE appraisals (TA775, TA942).^{139, 144, 151} The proportion of patients receiving living or deceased donor transplants, respectively, was sourced from RaDaR data in patients with C3G.¹⁷ Following transplantation, annual costs for immunosuppression medication to prevent graft rejection were applied, based on an NHS Blood and Transplant fact sheet used in multiple previous appraisals (TA775, TA890, TA942),^{139, 140, 144, 171} and it was assumed that these costs would continue to be incurred following graft failure.

The cost of dialysis was calculated using NHS reference costs, with HD assumed to be repeated three times per week and continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) assumed to be carried out daily.^{77, 78, 151} The proportions of patients receiving each type of dialysis was informed by RaDaR data in patients with C3G.¹⁷

Additionally, transport costs contribute to the resource use in CKD with patients receiving in-centre HD required to travel three times per week to receive treatment. An estimate for associated transportation costs was sourced from Liu et al. 2015,¹⁰⁹ a study estimating costs of HD from a UK payer perspective, as used in previous appraisals (TA937,¹⁴¹ TA809¹⁴⁷). Liu et al. derived a weighted transport cost estimate per in-centre HD session, accounting for multiple modes of transport with usage informed by a National Kidney Care Audit Patient Transport Survey.¹⁰⁹ After inflating the published value to 2022/23 costs,^{108, 109} transport costs of £63.40 was applied for all in-centre HD sessions in the model. Based on total activity reported in the 2023/2024 NHS reference costs, it was assumed that 96.8% of all HD patients would receive in-centre HD (96.8% hospital or satellite HD; 3.2% home HD).¹⁵¹

Table 50: Transplant and dialysis costs

	% of patients	Cost	Source
Weighted average transplant costs		£33,083.31 (one-off)	
Living donor transplant	34.2%	£34,295.02	Calculations as per TA775 ¹⁴⁴ using NHS reference costs, LA03A, LA10Z, LA11Z, LA12A, LA13A and LA14Z. ¹⁵¹ Percentage of living donor transplants based on RaDaR data in C3G. ¹⁷
Deceased donor transplant	65.8%	£32,453.22	Calculations as per TA775 ¹⁴⁴ using NHS reference costs, LA01A, LA02A, LA12A and LA13A. ¹⁵¹ Percentage of deceased donor transplants based on RaDaR data in C3G. ¹⁷
Post-transplant costs		£7,233.65 (per year)	

	% of patients	Cost	Source
Post-transplant	100%	£7,233.65	Annual cost of immunosuppression, NHS Blood and Transplant 2009; ¹⁷¹ inflated to 2022/2023 ¹⁰⁸
Weighted average dialysis costs		£42,237.61 (per year)	
CAPD	2.9%	£35,088.19	NHS reference costs, LD11A; ¹⁵¹ daily. ⁷⁷ Percentage of CAPD based on RaDaR data in C3G. ¹⁷
APD	11.8%	£40,832.46	NHS reference costs, LD12A and LD13A; ¹⁵¹ daily. ⁷⁷ Percentage of APD based on RaDaR data in C3G. ¹⁷
HD	85.3%	£33,072.88	NHS reference costs, weighted average of LD01A–LD10A; ¹⁵¹ 3x per week. ⁷⁷ Percentage of HD based on RaDaR data in C3G. ¹⁷
Transportation for patients on in-centre HD	85.3%	£9,605.07 (weighted to consider that 96.8% of all HD patients receive in-centre HD)	Liu et al. 2015; ¹⁰⁹ inflated to 2022/2023. ¹⁰⁸ This cost assumes 3.2% of HD patients receive HD at home, as per NHS reference costs, ¹⁵¹ and do not incur transport costs

Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; HD, haemodialysis; NHS, National Health Service; RaDaR, National Registry of Rare Kidney Diseases.

Sources: Novartis Data on File. 2024 (C3G RaDaR Priority Analysis, Interim Enrichment Report);¹⁷ NHS Blood and Transplant. 2009;¹⁷¹ NHS National Cost Collection 2023/2024;¹⁵¹ Liu et al. 2015;¹⁰⁹ PSSRU.¹⁰⁸

3.5.3 Miscellaneous unit costs and resource use

Vaccination and antibiotic costs

The use of complement inhibitors may predispose patients to serious infections with encapsulated bacteria. Based on the SmPC, patients treated with iptacopan must therefore be vaccinated against *N. meningitidis* and *S. pneumoniae*, while vaccination against *H. influenzae* type B is recommended.³⁰ In line with advice from UK nephrologists and existing UK guidelines for the prevention of meningococcal disease in adults receiving C5 inhibitors for aHUS, all patients treated with iptacopan within the model were assumed to receive vaccinations for *N. meningitidis* and *S. pneumoniae* every 5 years (modelled as 0.2 per year), and one vaccination for *H. influenzae* type B at the start of iptacopan treatment;^{27, 133} this is consistent with the assumptions in the previous NICE appraisal of iptacopan for PNH (TA1000).⁵² Vaccination costs were sourced from the BNF.⁵¹

Additionally, the cost of prophylactic antibiotics (penicillin, 250 mg b.i.d.) was also included for all patients treated with iptacopan, based on clinical expert advice and in line with standard UK practice for C5 inhibitors in aHUS.^{27, 40, 133} Vaccination and antibiotic resource use and costs associated with iptacopan are summarised in Table 51.

Table 51: Vaccination and antibiotic costs associated with iptacopan treatment

Vaccines and medications	Proportion of patients	Annual frequency	Unit cost	Cost source
<i>N. meningitidis</i> vaccines	100%	0.2	£105.00	BNF (Bexsero [£75.00] and Nimenrix [£30.00])
<i>S. pneumoniae</i> vaccine	100%	0.2	£49.10	BNF (Prevenar)

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Vaccines and medications	Proportion of patients	Annual frequency	Unit cost	Cost source
<i>H. influenzae type B</i> vaccine	100%	One-off cost	£37.76	BNF (Menitorix)
Penicillin	100%	730.50	£0.03	eMIT (Phenoxymethylpenicillin 250 mg tablets). Dosing 250 mg b.i.d. ¹³³
Total modelled costs				
One-off vaccination cost (<i>H. influenzae type B</i>)			£37.76	
Vaccination cost per cycle (<i>N. meningitidis</i> , <i>S. pneumoniae</i>)			£7.71	
Antibiotics cost per cycle			£6.04	

Abbreviations: BNF, British National Formulary; eMIT, electronic marketing information tool.

Source: BNF;⁵¹ eMIT 2024.¹⁵⁰

Adverse reaction unit costs and resource use

As described in Section 3.3.4, SAEs suspected to be related to iptacopan were included in the model. Given that these were mostly cases of pneumonia or consequences thereof, including sepsis (see Table 38), SAEs were costed as a weighted average of pneumonia and sepsis, based on 2023/2024 NHS reference costs (weighting based on total activity in NHS reference cost; Table 52).¹⁵¹ This approach was aligned with a clinical expert.⁴⁰

Table 52: Serious adverse event costs

HRG codes	Description	Weighted average unit cost ^a
DZ11K–DZ11V	Lobar, atypical or viral pneumonia	£2,819.03
DZ23H–DZ23N	Bronchopneumonia	
WJ06A–WJ06J	Sepsis	

^aWeighted by total activity of respective HRG codes in NHS reference costs.

Abbreviations: HRG, healthcare resource group.

Sources: NHS National Cost Collection 2023/2024.¹⁵¹

End-of-life costs

The model included end-of-life costs, in the form of hospital costs for terminal care in the 30 days prior to death. These costs were taken from Kerr et al. 2017,¹⁷⁴ which reported on end-of-life care in CKD in England, and inflated to 2022/2023.¹⁰⁸ This approach aligned to that in TA937.¹⁴¹ A one-off cost of £3,952.43 was therefore applied to patients entering the 'Death' state.

Cardiovascular event costs

As noted in Section 3.3.6, CV events were modelled as part of a scenario analysis, with the costs associated presented in Appendix K.

3.6 Severity

Expected general population QALYs were generated using England and Wales life tables from the Office for National Statistics¹⁵⁵ and general population utility values for the UK reported by Hernández-Alava et al. 2022.¹⁵⁷ These were compared with QALYs that people living with C3G would be expected to accrue with current treatment (i.e. SoC), which was obtained from the cost-effectiveness model results. Both absolute and proportional shortfalls were below NICE Company evidence submission for iptacopan for treating C3 glomerulopathy [ID6283]

thresholds for severity weighting, as summarised in Table 53, and so severity weights are not expected to be applicable for this submission.

Table 53: Summary of QALY shortfall analysis

Treatment	Expected general population QALYs	QALYs that people living with the condition would be expected to have with current treatment	Absolute shortfall	Proportional shortfall
SoC	21.00	15.13	5.87	0.28

Abbreviations: QALY: quality-adjusted life year; SoC: standard of care.

3.7 Uncertainty

The NICE Prioritisation Board confirmed that iptacopan for C3G meets the Highly Specialised Technologies (HST) routing criteria that relate to rarity of the disease (routing criteria 1 and 2).¹²² While the NICE evaluation takes place using the STA route, it is therefore vital that the challenges associated with an appraisal in a very rare condition, such as small sample sizes in clinical trials, and any resulting uncertainty are considered when evaluating the evidence.

Iptacopan is the first treatment to be appraised in C3G. Consequently, no HTA precedents exist. C3G-specific data sources to inform the model are scarce and where available, usually limited to smaller sample sizes. This may in turn give rise to uncertainty around mean parameter values. Where appropriate data were available, the model inputs were based on C3G-specific data, from the iptacopan clinical trial programme in C3G or the C3G cohort of RaDaR. To ensure model inputs were clinically appropriate, clinical input from UK experts in C3G was sought to validate all key parameters (as detailed in Section 3.13).

C3G is an ultra-rare disease and generating comparative efficacy data can be challenging as the number of patients included in clinical trials is typically small. While the methods applied to generate comparative efficacy data for this submission are in line with best practice, the ultra-rare nature of the disease leads to uncertainty in the estimates.

Novartis asks the NICE Committee to consider the strength of the data presented in light of the rarity of the condition. Flexibility in NICE's STA process is therefore expected to be relevant in this appraisal.

3.8 Summary of base-case analysis inputs and assumptions

3.8.1 Summary of base-case analysis inputs

A summary of inputs used in the deterministic base case is presented in Table 54.

Table 54: Summary of base-case inputs

Variable	Value	Reference to section in submission
Model settings		
Patient population	Adults with C3G	Section 3.2.2
Model structure	Markov model	

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Variable	Value	Reference to section in submission
Time horizon	Lifetime horizon (up to age 100; base case: 72.1 years)	
Cycle length	3 months	
Perspective	NHS and PSS	
Discounting per year of costs and utilities	Annual rate of 3.5% for costs and outcomes	
Treatment waning effect?	None	
Baseline characteristics		
Mean age, years	27.9	Section 3.3.1
Females, %	36.5	
Mean eGFR	92.8	
Baseline CKD stage distribution		
CKD stage 1, %	58.1	Section 3.3.1
CKD stage 2, %	23.0	
CKD stage 3a, %	6.8	
CKD stage 3b, %	9.5	
CKD stage 4, %	2.7	
Disease progression		
SoC rate of eGFR decline per year	-7.224	Section 3.3.2
Iptacopan rate of eGFR decline per year	-0.289	
Transition probabilities per cycle for SoC, %		
CKD stage 1 -> stage 2	4.22	Section 3.3.2
CKD stage 2 -> stage 3a	7.71	
CKD stage 3a -> stage 3b	11.34	
CKD stage 3b -> stage 4	11.34	
CKD stage 4 -> stage 5 (pre-KRT)	14.86	
CKD stage 5 (pre-KRT) -> KRT	38.43	
Transition probabilities per cycle for iptacopan, %		
CKD stage 1 -> stage 2	0.17	Section 3.3.2
CKD stage 2 -> stage 3a	0.32	
CKD stage 3a -> stage 3b	0.48	
CKD stage 3b -> stage 4	0.48	
CKD stage 4 -> stage 5 (pre-KRT)	0.64	
CKD stage 5 (pre-KRT) -> KRT	1.92	
KRT		
KRT threshold, eGFR (mL/min/1.73m²)	7.6	Section 3.3.2
Proportion of patients eligible for a transplant, %	83.2 (ineligible: 16.8)	
Proportion of patients receiving pre-emptive transplant as their first KRT modality, %	18.4	
Assumed maximum age for receipt of transplant, years	80	

Variable	Value	Reference to section in submission
Probability per cycle of receiving a transplant (excluding pre-emptive transplants), %	8.7	
Probability per cycle of having graft failure, %	2.6	
Proportion of patients eligible for a subsequent transplant, after graft failure of their 1 st transplant, %	83.2	
Iptacopan discontinuation		
Probability of all-cause discontinuation (prior to kidney failure) per cycle, %	1.57	Section 3.3.3
Discontinuation at kidney failure		
Iptacopan, SGLT2i, MMF, CS	At KRT threshold	Section 3.3.3
ACEi, ARB	No discontinuation	
AEs		
Probability of SAEs (iptacopan arm) per cycle, %	0.66	Section 3.3.4
Mortality		
SMR for CKD stages 1–4	1.32	Section 3.3.5
SMR for CKD stage 5 (pre-KRT), dialysis, post-transplant	3.99	
Health state utility multipliers ^a		
CKD stage 1	0.99	Section 3.4.4
CKD stage 2	0.99	
CKD stage 3a	0.94	
CKD stage 3b	0.94	
CKD stage 4	0.92	
CKD stage 5 (pre-KRT)	0.88	
Dialysis	0.54 (weighted average HD and PD)	
Post-transplant	0.82	
AE utility decrement		
Utility decrement for serious infections	0.156	Section 3.4.4
Disutility duration, days	32.1	
Treatment acquisition costs		
Iptacopan acquisition costs per year (at PAS price)		Section 3.5.1
Patients on ACEi, %	47.3	
Patients on ARB, %	52.7	
Patients on SGLT2i, %	5.4	
Patients on MMF, %	36.5	
Patients on CS, %	32.4	
SoC acquisition costs per year	£91.95	

Variable	Value	Reference to section in submission
Disease monitoring unit costs		
Nephrologist visit	£206.69	Section 3.5.2
eGFR test	£1.53	
Blood pressure check	£5.67	
UPCR or UACR test	£1.53	
Complement biomarker tests	£2.98	
Full blood count	£2.98	
Liver function tests	£1.53	
Disease monitoring visits per year		
CKD stage 1	2	Section 3.5.2
CKD stage 2	2	
CKD stage 3a	3	
CKD stage 3b	4	
CKD stage 4	5	
CKD stage 5 (pre-KRT)	5	
Dialysis	3	
Post-transplant	4	
Transplant and dialysis costs		
Living donor transplant, % of transplanted patients	34.2	Section 3.5.2
Deceased donor transplant, % of transplanted patients	65.8	
Transplant costs, one off	£33,083.31	
Post-transplant immunosuppression costs, per year	£7,233.65	
CAPD, % of patients on dialysis	2.9	
APD, % of patients on dialysis	11.8	
HD, % of patients on dialysis	85.3	
Dialysis costs, per year	£42,237.61	
Vaccination and antibiotic costs		
One-off vaccination costs	£37.76	Section 3.5.3
Vaccination costs, per cycle	£7.71	
Antibiotics costs, per cycle	£6.04	
AE costs		
AE management costs, per SAE	£2,819.03	Section 3.5.3
End-of-life costs		
End-of-life costs, one off	£3,952.43	Section 3.5.3
CV events		
Include CV events?	No	Section 3.3.6

^aApplied to age- and sex-matched general population utility values.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; APD, automated peritoneal dialysis; ARB, angiotensin receptor blocker; C3G, complement 3 glomerulopathy; CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; CS, corticosteroid; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HD, haemodialysis; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; PAS, patient access scheme; SAE, serious adverse event; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SMR, standardised mortality ratio; SoC, standard of care; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

3.8.2 Assumptions

A summary of base-case assumptions is provided in Table 55.

Table 55. Assumptions in model base case

Assumption	Justification
All patients were assumed to be at the midpoint of each CKD stage	This is a simplifying assumption which assumes uniform distribution of patients within a CKD stage. This assumption allowed calculation of the mean eGFR value for each CKD stage, followed by estimation of the time to move between states, which was calculated as the time taken for eGFR to decline from the midpoint of the current CKD stage to the midpoint of the next CKD stage
eGFR was assumed to change at a constant rate, regardless of CKD stage	While in clinical practice it is expected that eGFR decline may vary over the course of disease, the sample size of the iptacopan trials in C3G did not permit estimation of CKD stage-dependent eGFR decline rates. As such, a simplifying assumption that speed of progression is independent of CKD stage and constant over the course of disease was applied
Transplants were assumed to occur at a constant rate	It is assumed that in patients on dialysis who are eligible for a transplant, the rate of transplant is constant. This is a simplifying assumption. Assuming a constant rate allows the model to avoid using tunnel states to model complex time-dependency
People aged ≥80 years were assumed to not receive a transplant	This assumption was made in line with NICE appraisal TA942 in CKD ¹³⁹
Graft failure was assumed to occur at a constant rate	This is a simplifying assumption. To incorporate time dependency in graft failure would require the use of tunnel states to track patients following their transplant, introducing additional complexity in the model
It was assumed that cost for immunosuppression would continue to be incurred following graft failure	This assumption was included as patients are expected to require immunosuppression following graft failure
Patients discontinuing iptacopan prior to kidney failure were assumed to receive SoC alone	This assumption reflects the current lack of alternative treatment options in C3G
Patients were assumed to stop iptacopan treatment at the point of commencing KRT. Patients were also assumed to stop SoC at the point of commencing KRT, except for ACEis/ARBs which are continued during KRT	This assumption was based on expert clinical opinion ²⁷
Standardised mortality ratios from people with rare kidney diseases as captured in RaDaR can be applied to a C3G cohort	Estimates of relative mortality for patients with C3G by CKD stage or on KRT were not identified. The utilised source, representing data from a broader RaDaR

Assumption	Justification
	cohort, ¹⁴ was recommended by clinical experts for use in the economic model ²⁷
All patients treated with iptacopan within the model were assumed to receive vaccinations for <i>N. meningitidis</i> and <i>S. pneumoniae</i> every 5 years (while on iptacopan), one vaccination for <i>H. influenzae</i> type B at the start of iptacopan treatment, and ongoing prophylactic antibiotic treatment alongside iptacopan	In line with advice from UK clinicians and existing UK guidelines for C5 inhibitors in aHUS. ^{27, 133} This is consistent with the assumptions in the previous NICE appraisal of iptacopan for PNH (TA1000) ⁵²

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; aHUS, atypical haemolytic uraemic syndrome; ARB, angiotensin receptor blocker; C3G, complement 3 glomerulopathy; C5, complement component 5; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; NICE, National Institute for health and Care Excellence; PNH, paroxysmal nocturnal haemoglobinuria; RaDaR, National Registry of Rare Kidney Diseases; UK, United Kingdom.

3.9 Base-case results

3.9.1 Base-case incremental cost-effectiveness analysis results

The deterministic base-case results expressed in terms of incremental costs, incremental LYGs, incremental QALYs and ICERs are presented in Table 56. At the PAS price, iptacopan + SoC was associated with 1.74 incremental QALYs at an incremental cost of [REDACTED] versus SoC alone. The resulting ICER versus SoC is [REDACTED] per QALY gained (Table 56).

The incremental net-health benefit (INHB) of iptacopan at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 is presented in Table 57. INHB represents the sum of the incremental QALYs and incremental costs valued in health terms, with a positive INHB indicating the intervention is cost-effective at the selected WTP threshold. INHB was selected in line with the preference expressed in the NICE manual.³⁹ In the deterministic base-case, INHB for iptacopan + SoC versus SoC was -[REDACTED] and -[REDACTED] QALYs at a WTP threshold of £20,000 and £30,000, respectively.

Disaggregated costs and outcomes are presented in Appendix H. Incremental costs for iptacopan were driven by drug acquisition costs; whereas the largest cost savings were accrued from lower medical resource use associated with dialysis. Incremental QALY gains for iptacopan were mainly accrued in CKD stages 1 and 2, reflecting its effect on slowing the progression of C3G.

[REDACTED]

Table 56: Deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
SoC	£355,162	21.11	15.13	-	-	-	-
Iptacopan + SoC	████████	21.59	16.88	████████	0.48	1.74	████████

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SoC, standard of care.

Table 57: Deterministic net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
SoC	£355,162	15.13	-	-	-	-
Iptacopan + SoC	████████	16.88	████████	1.74	-████████	-████████

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care.

3.10 Exploring uncertainty

As detailed in Section 3.7, model parameters were associated with uncertainty as would be expected in an ultra-rare disease. In order to assess the impact of parameter uncertainty on the economic model results, both probabilistic and deterministic sensitivity analyses were conducted, the results of which are presented in Sections 3.10.1 and 3.10.2, respectively. In addition, key assumptions in the model were explored in several scenario analyses, the results of which are presented in Section 3.10.3.

3.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the impact of uncertainty around parameter values on the results of the model base case. Where data were available, probability distributions were assigned to parameters, to characterise uncertainty associated with the precision of the mean values, based on the nature of each parameter. Where empirical probability distributions were not available, the standard error was assumed to take a value equal to 10% of that of the mean. The base-case ICER stabilised from approximately ~150 iterations onwards (see Figure 28 for the probabilistic ICER convergence plot), therefore 1000 iterations were considered sufficient without incurring a significant run-time.

The probabilistic base-case results expressed in terms of incremental costs, incremental LYGs, incremental QALYs and ICERs are presented in Table 58 and the probabilistic INHB at WTP thresholds of £20,000 and £30,000 are presented in Table 59. The probabilistic ICER of iptacopan and SoC versus SoC is [REDACTED] per QALY gained, falling within [REDACTED]% of the deterministic ICER, indicating that cost-effectiveness results were consistent.

The cost-effectiveness plane and acceptability curves are presented in Figure 29 and Figure 30, respectively.

Table 58: Probabilistic base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
SoC	£351,750	21.12	15.17	-	-	-	-
Iptacopan + SoC	████████	21.60	16.88	████████	0.48	1.71	████████

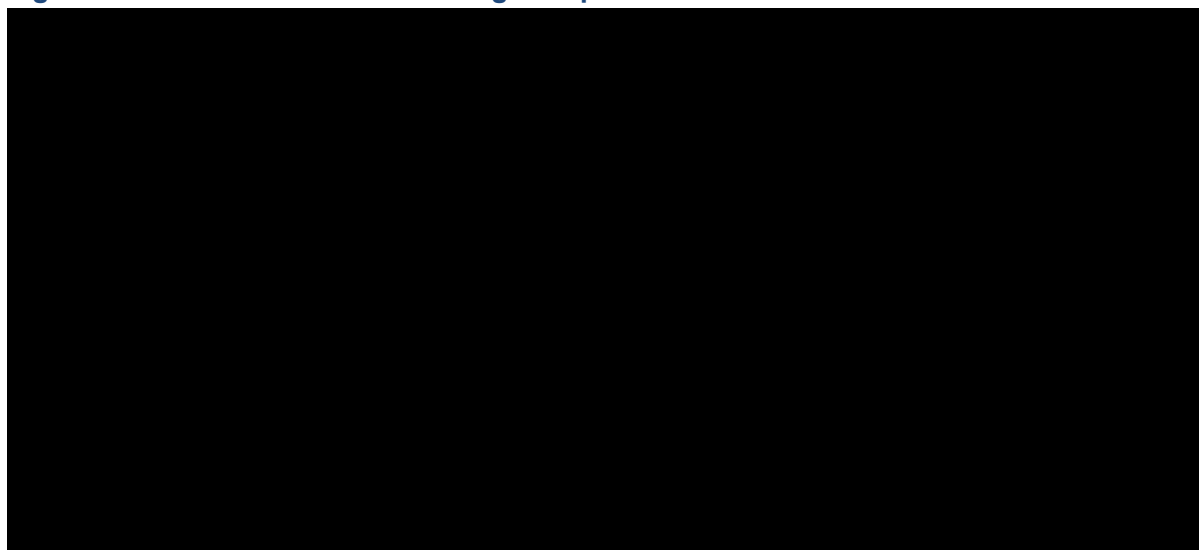
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SoC, standard of care.

Table 59: Probabilistic net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
SoC	£351,750	15.17	-	-	-	-
Iptacopan + SoC	████████	16.88	████████	1.71	-████	-████

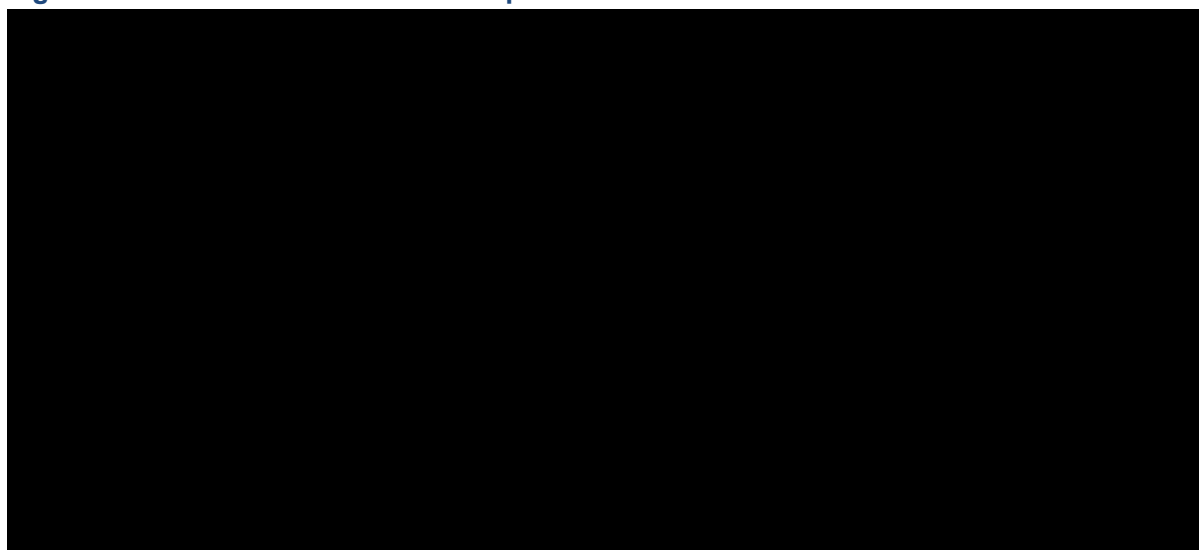
Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care.

Figure 28: Probabilistic ICER convergence plot



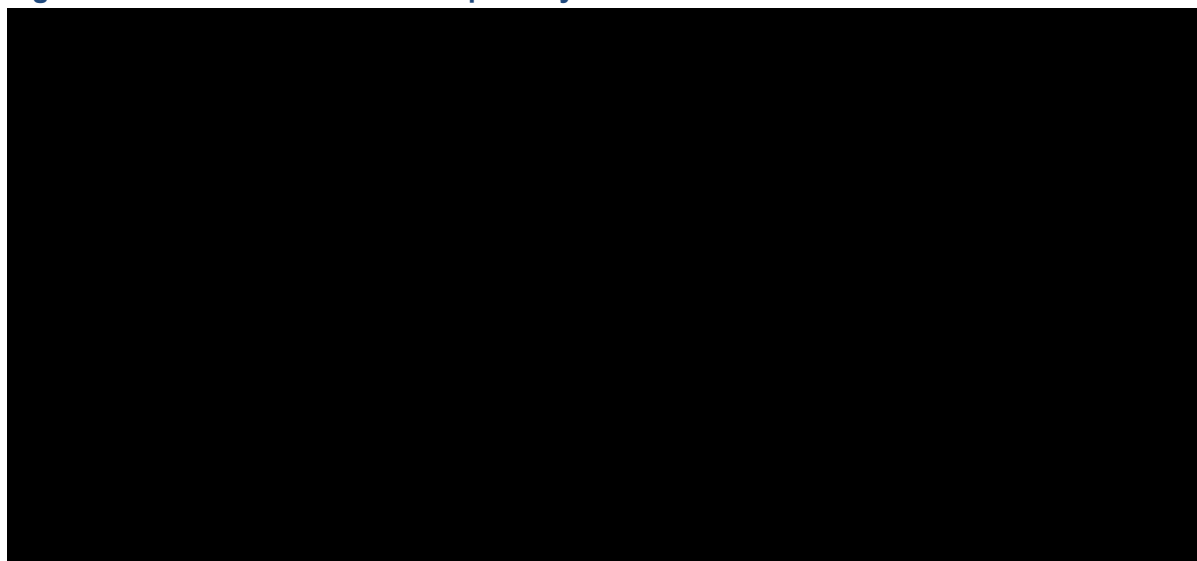
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC, standard of care.

Figure 29: Cost-effectiveness scatter plot from base-case PSA



Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 30: Cost-effectiveness acceptability curve from base-case PSA



Abbreviations: PSA: probabilistic sensitivity analysis; SoC: standard of care.

3.10.2 Deterministic sensitivity analysis

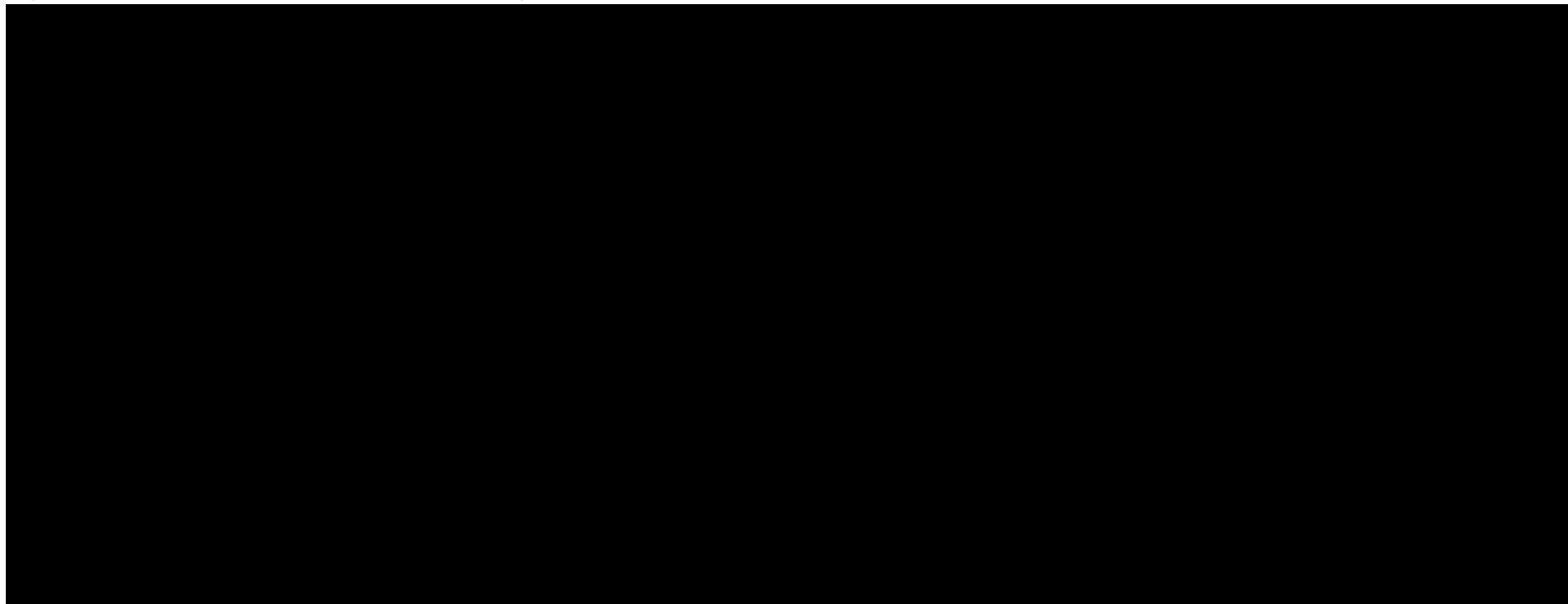
To further assess the robustness of the base-case model results, deterministic sensitivity analyses (DSA) were conducted by varying one model input at a time to assess which parameters had the largest impact on the ICER. Some parameters that do not have any uncertainty associated with the input value were excluded from the DSA.

Details on the parameters and ranges tested in the DSA are provided in Appendix L.

For clinical and utility parameters, 95% CI were used, which were sourced from published data, where available, and calculated where data were not available. For other parameters, the variation was assumed to be a set percentage of the mean ($\pm 20\%$); upper and lower values were either calculated directly by adding or subtracting the respective percentage (for the cost inputs), or by using this to further calculate appropriate variations (in the case for the lognormal variation of the mortality HRs).

Results of the DSA show that the most influential parameter on the base-case ICER is the iptacopan treatment effect, with APPEAR-C3G utilities the next most influential parameters (Figure 31).

Figure 31: DSA tornado plot for absolute change in ICER



Abbreviations: C3G, complement 3 glomerulopathy; DSA: deterministic sensitivity analysis; eGFR, estimated glomerular filtration rate; HD, haemodialysis; HSUV, health-state utility value; ICER, incremental cost-effectiveness ratio; SoC, standard of care.

3.10.3 Scenario analysis

Scenario analyses were conducted to test the robustness of the model results to alternative model inputs and assumptions.

A list of all scenario analyses and their results are presented in Table 60. These results show that the scenario analysis with the greatest impact on the base-case ICER was scenario #3, utilising eGFR slope data from the 6-month placebo-controlled period of APPEAR-C3G, which increased the ICER by █%. However, as noted in Section 3.3.2, this result should be interpreted with caution, since UK clinicians advised that predictions of SoC arm disease progression in this scenario lacked clinical validity (model-predicted median time to kidney failure with SoC 22.8 years, compared with approximately 10 years based on literature and advisors' clinical experience).^{27, 40}

All other scenario analyses had a relatively minor impact, with impact on the ICER less than █% (in either direction) (Table 60).

Table 60: Results of deterministic scenario analyses

#	Scenario analysis description	Base case description	Incremental costs	Incremental QALYs	ICER	% ICER change from base case
-	Base case (deterministic)	-	██████	1.74	██████	N/A
Model settings						
1	CV events included	CV events not included	██████	1.74	██████	██████
Model inputs						
2	eGFR slope data from pooled population (APPEAR-C3G and Phase 2 native kidney cohort; up to 4.7 years iptacopan treatment duration)	eGFR slope data from APPEAR-C3G population (up to 2 years iptacopan treatment duration)	██████	1.62	██████	██████
3 ^a	eGFR slope data from APPEAR-C3G placebo comparison (based on 6 months of data)	eGFR slope data from APPEAR-C3G population (up to 2 years iptacopan treatment duration)	██████	1.36	██████	██████
4	Baseline characteristics and initial health state distribution from RaDaR	Baseline characteristics and initial health state distribution from APPEAR-C3G	██████	1.66	██████	██████
5	CKD stage transitions at upper eGFR bound of CKD stage	CKD stage transitions at midpoint of CKD stage, except for transition to KRT at KRT threshold	██████	1.75	██████	██████
6	Transplant eligibility of 93.18% for initial and 73.18% for subsequent transplants	Transplant eligibility of 83.2% for initial and subsequent transplants	██████	1.73	██████	██████
7	No maximum age for transplant	Maximum age for receipt of transplant 80 years	██████	1.74	██████	██████
8	Discontinuation of iptacopan, SGLT2i, MMF, CS upon	Discontinuation of iptacopan, SGLT2i, MMF, CS upon	██████	1.72	██████	██████

#	Scenario analysis description	Base case description	Incremental costs	Incremental QALYs	ICER	% ICER change from base case
	entering CKD stage 5 (eGFR≤15 mL/min/1.73m ²)	reaching KRT threshold (eGFR ≤7.6 mL/min/1.73m ²)				
9	Mortality HRs based on Go et al. 2004	Mortality SMRs based on Wong et al. 2024	██████	1.81	██████	██████
10	CKD stage 1–4 utility values from Jesky et al. 2016	CKD stage 1–4 utility values from APPEAR-C3G	██████	1.82	██████	██████
11	Proportion of patients receiving SGLT2i assumed as 50%	Proportion of patients receiving SGLT2i based on APPEAR-C3G (5.4%)	██████	1.74	██████	██████
12	Healthcare resource use based on Kent et al. 2015; monitoring costs set to 0	Disease monitoring resource use based on UK advisory board survey	██████	1.74	██████	██████
13	Disease monitoring frequency based on NICE guideline NG203	Disease monitoring frequency based on UK advisory board survey	██████	1.74	██████	██████
14	KRT threshold of eGFR ≤10 mL/min/1.73m ²	KRT threshold of eGFR ≤7.6 mL/min/1.73m ²	██████	1.74	██████	██████
15	Iptacopan SAEs counted as 9 individual events in 189.9 patient years	Iptacopan SAEs counted as 5 episodes in 189.9 patient years	██████	1.74	██████	██████

Footnotes: Scenario #3 should be interpreted with caution, since UK clinicians advised that predictions of SoC arm disease progression in this scenario lacked clinical validity (model-predicted median time to kidney failure with SoC 22.8 years, compared with approximately 10 years based on literature and advisors' clinical experience).^{27, 40}

Abbreviations: CKD, chronic kidney disease; CS, corticosteroid; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; QALY, quality-adjust life year; RaDaR, National Registry of Rare Kidney Diseases; SAE, serious adverse event; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SMR, standardised mortality ratio.

Sources: Go et al. 2004;⁸⁴ Jesky et al. 2016;¹³⁵ Kent et al. 2015;¹⁷⁰ Wong et al. 2024;¹⁴ NICE (NG203). 2021.¹¹

3.11 Subgroup analysis

As described in Section 1.1, this submission covers the full expected marketing authorisation for iptacopan in C3G.

Economic modelling has been based on iptacopan trial data from patients with native kidney C3G, based on the Phase 3 APPEAR-C3G study. For patients with post-transplant recurrence, the sample size of the Phase 2 clinical trial cohort (N=11) did not permit a robust economic analysis. However, given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients.^{27, 40} Furthermore, the approach to model only a native kidney population aligns with that taken in previous NICE appraisals in other chronic kidney diseases, with the NICE recommendations for these treatments not excluding transplanted patients even where transplanted patients were excluded from the clinical trials (Appendix E, Table 12).

Whilst a distinction between C3GN and DDD is made based on kidney tissue biopsy findings,¹³³ the clinical presentation, disease course, and management of these C3G subtypes are generally considered to be consistent.^{5, 18, 19, 43} Similarly, CFHR5 nephropathy is a subtype of C3GN, caused by a genetic mutation endemic to people of Cypriot origin.^{44, 45} Consequently, the clinical and cost-effectiveness of iptacopan are not expected to differ between people with C3GN (including CFHR5 nephropathy) and people with DDD.⁴⁰ Economic analyses for subgroups are therefore not presented in this submission.

3.12 Benefits not captured in the QALY calculation

The economic analysis has attempted to include all the potential benefits related to iptacopan within the QALY calculation. There are, however, several potential benefits of treatment with iptacopan which are not captured within the assessment.

As discussed in Section 1.3.6, C3G has a large impact on patient and carer quality of life, with the impact of the symptoms themselves, their effects on a person's ability to participate and complete daily activities, and the uncertainty surrounding disease progression and lack of treatment options impacting mental health.^{7, 93} This was also highlighted by several UK patient organisations during the draft scope consultation of iptacopan for C3G.¹⁰⁴ The disease impacts may not be fully captured in standard generic HRQoL measures such as EQ-5D, and the clinical benefit of iptacopan should therefore be considered in this context.

C3G also impacts on patients' and carers' time and productivity. People receiving dialysis require multiple sessions per week, with each session taking multiple hours.⁷⁷ Individuals with C3G, as well as their carers, may therefore have to reduce hours at work or in education as a result of their disease.^{7, 93} A patient organisation described in their response to the draft scope consultation how affected individuals have to "fit a life around dialysis treatment", with in-centre dialysis "tak[ing] out three days a week of normal life", once transport time, waiting time, and the four-hour treatment duration are taken into account.¹⁰⁴ Young patients have reported not being able to attend education regularly, impacting their future career opportunities.⁹³ These impacts are likely insufficiently captured in the QALY calculation. Iptacopan, by delaying kidney failure and the need for KRT, may therefore be able to provide additional benefits not captured in the economic analysis.

The expected reduced need for KRT with iptacopan has the potential to provide further benefits to people with kidney diseases more broadly and the NHS. As noted in Section 1.3.6, the current wait time for kidney transplants in the UK is 2–3 years.¹⁰⁶ By reducing the number of people requiring a transplant due to their C3G, the availability of iptacopan may be able to reduce the number of patients on waiting lists and speed up access for other patients in need of a kidney transplant. A report from Kidney Research UK in 2023 also highlighted capacity constraints for dialysis in the UK, estimating that capacity would need to grow by 400% by 2033 to meet increasing demand.¹⁰⁶ Iptacopan, by delaying the time to kidney failure, may be able to reduce the increase in the demand for dialysis. These effects are not captured in the QALY calculation.

Finally, the availability of iptacopan has the potential to reduce health inequalities in the NHS. As highlighted in Section 1.4, there is considerable inequality across ethnic groups with regards to access to kidney transplants, with individuals of Black and Asian descent more likely to face much lengthier wait times.^{106, 118} Equitable access for all ethnicities to iptacopan, with its potential to reduce the need for transplants, would address this inequality for people with C3G.

3.13 Validation

3.13.1 Validation of cost-effectiveness analysis

Clinical and health economist validation

Novartis UK held two advisory boards with nine (April 2022) and ten (November 2024) UK clinicians with experience in treating patients with C3G in NHS clinical practice; insights from both advisory boards informed this submission.^{26, 27} Advisors provided their views on the current SoC and treatment landscape for C3G, level of unmet need, and iptacopan trial data, as well as clinical input for modelling disease progression and disease management before and after kidney failure.

Additionally, calls with two individual UK clinicians were conducted to clarify individual points of uncertainty relating to the submission, and model validation was undertaken in a joint call with one clinical and one external health economics expert from the UK.⁴⁰ Model validation covered selection of the base case for modelling disease progression and treatment effect, health state utility values, health state costs, and AEs, as well as validation of clinical outputs of the draft economic model.

The modelling approach, inputs and assumptions presented in this submission took into account the feedback received by clinical and health economics experts, as detailed throughout Section 3.

Internal technical validation

Once the model was completed, in alignment with best practice, an independent team of health economists who were not involved in programming the model performed a full technical quality control check which was conducted by completing two checklists, based on the published TECH-VER checklist:¹⁷⁵

- **Quality control checklist**, which involved checking through every cell of the model to ensure that all formulae are correct, that macros have been coded correctly, that everything is referenced correctly, that there are no spelling or grammar mistakes, and that the formatting is consistent

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- **Internal validation checklist**, which involved setting up different scenarios to check that the model responds in the appropriate manner; for example, when all utility values are set to 1, the LYs should equal the QALYs. The model is pushed to the extremes to test whether it reacts to extreme values in an expected way

Together these checklists provided quality control and internal validation of the model through a documented review process. In addition, an independent analyst performed a full input quality check, checking all model inputs against their original source.

3.14 Interpretation and conclusions of economic evidence

3.14.1 Cost effectiveness of iptacopan in adults with C3G

At the PAS price, the deterministic base-case analysis showed that iptacopan + SoC was associated with 1.74 incremental QALYs at an incremental cost of [REDACTED] versus SoC alone. The resulting ICER was [REDACTED] per QALY gained.

[REDACTED]	
[REDACTED]	
[REDACTED]	

3.14.2 Strengths and limitations

The model was developed in line with the NICE reference case.³⁹ The selected model structure, which includes health states for CKD stages and KRT, was aligned with several prior appraisals in other chronic kidney diseases which also used eGFR data to model disease progression (see Table 31). The modelling approach and key inputs were discussed with UK clinicians with expertise and experience in treating C3G in NHS clinical practice, and their input in two advisory boards and other validation meetings (see Section 3.13.1) guided the selection of the base case inputs and confirmed the validity of the approaches.^{26, 27, 40}

While C3G is an ultra-rare disease with associated evidence generation challenges, key model inputs were informed by evidence from the population of interest. Efficacy and safety inputs came from the clinical trial programme for iptacopan in C3G. The use of iptacopan within APPEAR-C3G matches its intended indication, and therefore the data incorporated into the model can be expected to align to clinical practice.³³

Clinical experts confirmed that model predictions for the SoC arm in the base case (such as time to kidney failure) aligned well to current real-world evidence from RaDaR, a UK-specific source of C3G patient data and therefore of high relevance to the modelled population.^{17, 27, 40}

Although some model inputs had to be taken from the broader CKD literature, utility values for health states prior to kidney failure could be sourced from APPEAR-C3G. Model inputs relating to KRT, including dialysis, transplant, and graft failure, were mostly informed by analyses of the C3G cohort in RaDaR, which provides UK-specific longitudinal data from the population of interest for this appraisal.^{17, 59} RaDaR, the largest rare kidney disease registry in the world,¹⁴ is considered the most clinically relevant data source outside of the clinical trial programme, and the use of UK-specific data in the model, despite the ultra-rare nature of C3G and relative lack of data worldwide, strengthen the validity of the model results.

The economic analysis had some limitations. As discussed in Section 3.7, C3G is an ultra-rare disease and iptacopan is the first targeted treatment, and as such, data sources and precedents to inform the model are limited. Where relevant, information from previous NICE appraisals in other chronic kidney diseases was utilised to inform this submission. NICE are asked to apply flexibility in the STA process to enable timely and equitable access for people with a rare disease of this nature, when compared to products being assessed through the STA process for conditions with a much higher prevalence.

Due to ethical reasons, the placebo-controlled period of APPEAR-C3G was limited to six months.³³ Placebo arm data from APPEAR-C3G are therefore limited to a relatively short period, and predictions of time to kidney failure based on the placebo arm data were deemed clinically implausible by UK clinicians.^{27, 40} The model therefore does not use data from the placebo-controlled period of the trial in the base case. However, the comparison of on-iptacopan versus pre-iptacopan, which was modelled instead, allowed for the use of data from a greater number of patients and a longer treatment period; eGFR slopes used in the base case were generated from 74 patients with up to 2.5 years of pre-iptacopan and up to 2 years of on-iptacopan data.¹²⁴ As noted above, the pre-iptacopan data from this analysis align well with data from RaDaR, and clinical validity was further supported by UK clinical experts.^{27, 40}

Economic modelling in this submission is based on data from patients with native kidney disease, in line with previous appraisals in various other chronic kidney diseases which did not model post-transplant cohorts. For patients with post-transplant recurrence of C3G, the sample size of the Phase 2 clinical trial cohort and absence of a comparator arm did not permit a robust economic analysis. However, the results from the Phase 2 and extension studies support the clinical effectiveness of iptacopan in patients with post-transplant recurrence, and clinical advisors confirmed they expected iptacopan to be effective in patients with post-transplant recurrence.^{27, 34, 38} Therefore, though not directly modelled, it is expected that the benefits demonstrated by the economic model would translate into this cohort with high unmet need.

3.14.3 Conclusions on cost-effectiveness

The results of the base case cost-effectiveness analysis indicate that iptacopan plus SoC was associated with 1.74 QALYs versus SoC alone. [REDACTED]

Given the current absence of effective disease-modifying treatment options for C3G, there remains a critical unmet need for targeted therapies in this population. Individuals with C3G, carers, patient organisation representatives and clinicians have expressed a need for improved treatment options, given that current treatment with SoC does not prevent disease progression to kidney failure.^{26, 27, 93, 104} Iptacopan is therefore expected to provide a vital treatment option for people with C3G.

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Single technology appraisal

Iptacopan for treating complement 3 glomerulopathy (ID6283)

Addendum to company evidence submission

June 2025

File name	Version	Contains confidential information	Date
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1 Background to addendum

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
			[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

2 Cost-effectiveness results

2.1 Base-case results

2.1.1 Base-case incremental cost-effectiveness analysis results

The deterministic base-case results expressed in terms of incremental costs, incremental LYGs, incremental QALYs and ICERs are presented in Table 2. [REDACTED], iptacopan + SoC is associated with 1.74 incremental QALYs at an incremental cost of [REDACTED] versus SoC alone. The resulting ICER versus SoC is [REDACTED] per QALY gained (Table 2).

The incremental net-health benefit (INHB) of iptacopan at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 is presented in Table 3. INHB represents the sum of the incremental QALYs and incremental costs valued in health terms, with a positive INHB indicating the intervention is cost-effective at the selected WTP threshold. INHB was selected in line with the preference expressed in the NICE manual. In the deterministic base-case, INHB for iptacopan + SoC versus SoC was [REDACTED] and [REDACTED] QALYs at a WTP threshold of £20,000 and £30,000, respectively.

Table 1: Deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
SoC	£355,162	21.11	15.13	-	-	-	-
Iptacopan + SoC		21.59	16.88		0.48	1.74	

Base case incorporates cost of iptacopan wastage, implemented in response to clarification question B15.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SoC, standard of care.

Table 2: Deterministic net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
SoC	£355,162	15.13	-	-	-	-
Iptacopan + SoC		16.88		1.74		

Base case incorporates cost of iptacopan wastage, implemented in response to clarification question B15.

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care.

2.2 Exploring uncertainty

2.2.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the impact of uncertainty around parameter values on the results of the model base case. Where data were available, probability distributions were assigned to parameters, to characterise uncertainty associated with the precision of the mean values, based on the nature of each parameter. Where empirical probability distributions were not available, the standard error was assumed to take a value equal to 10% of that of the mean. The PSA was run with 1000 iterations, with the probabilistic ICER convergence plot shown in Figure 1.

The probabilistic base-case results expressed in terms of incremental costs, incremental LYGs, incremental QALYs and ICERs are presented in Table 4 and the probabilistic INHB at WTP thresholds of £20,000 and £30,000 are presented in Table 5. The probabilistic ICER of iptacopan and SoC versus SoC [REDACTED] is [REDACTED] per QALY gained, falling within [REDACTED]% of the deterministic ICER.

Please note that errors in relation to the PSA identified by the EAG in their review of the company's economic model (as described in the EAG report), as well as one further PSA error subsequently identified by the company, were corrected prior to running these analyses. The implemented corrections are described in the company factual accuracy check comments document as submitted to NICE on 11th June 2025, 'Section 5: Company modelling inaccuracies'.

The discrepancy between the deterministic and probabilistic base-case ICERs was investigated and found to be connected to structural capabilities of the model which prevent positive eGFR slopes, due to the clinical implausibility of eGFR increasing continuously over the lifetime horizon. The iptacopan eGFR slope (cell I11, Clinical data tab) is calculated from the SoC eGFR slope and the iptacopan treatment effect. In this calculation, the iptacopan eGFR slope is capped at a maximum value of 0, i.e. not allowing positive eGFR slope values. When both the SoC eGFR slope and iptacopan treatment effect are varied, for all simulations which would result in a positive iptacopan eGFR slope, the iptacopan eGFR slope is thus capped at 0. For these simulations, the ICER is approximately [REDACTED]% below the deterministic value. For simulations where capping is not applicable and the iptacopan eGFR slope is a more negative value than the deterministic value, there is a significant impact on the ICER, due to its sensitivity to the iptacopan eGFR slope. As a result, in the calculation of the average cumulative ICER across many simulations, the large ICERs due to the uncapped eGFR slope values dominate vs the smaller ICERs from the capped eGFR slope values.

The cost-effectiveness plane and acceptability curves are presented in Figure 2 and Figure 3, respectively.

Table 3: Probabilistic base case results [REDACTED]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
SoC	£355,737	21.12	15.15	-		-	-
Iptacopan + SoC	[REDACTED]	21.55	16.67	[REDACTED]	0.43	1.53	[REDACTED]

Base case incorporates cost of iptacopan wastage, implemented in response to clarification question B15.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SoC, standard of care.

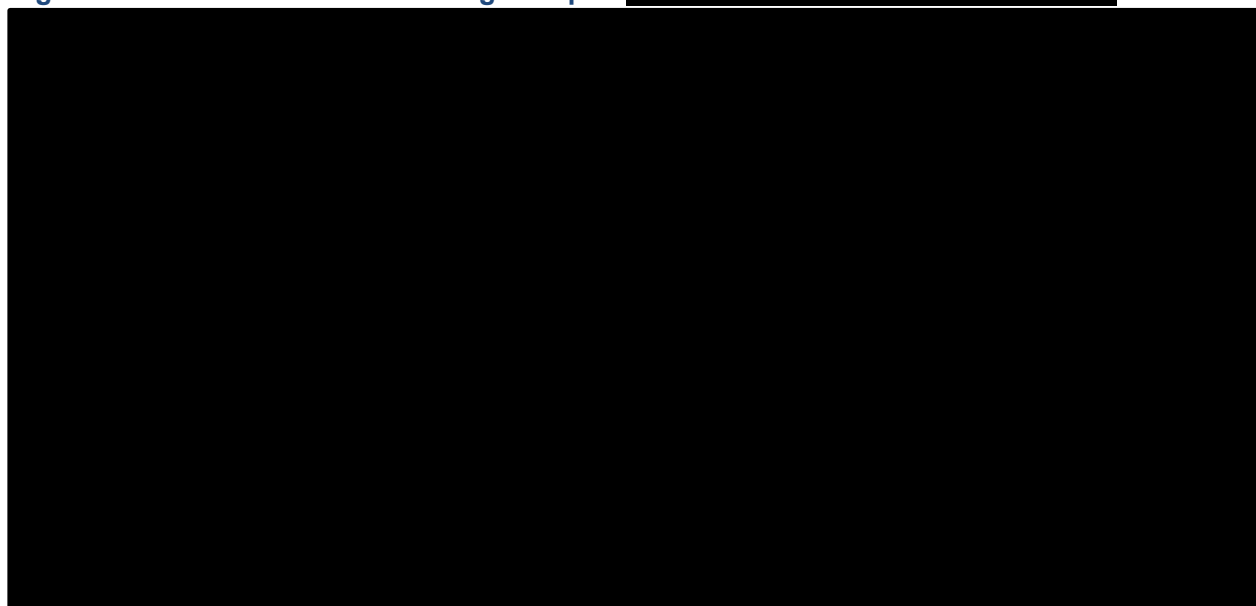
Table 4: Probabilistic net health benefit [REDACTED]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
SoC	£355,737	15.15	-	-	-	-
Iptacopan + SoC	[REDACTED]	16.67	[REDACTED]	1.53	[REDACTED]	[REDACTED]

Base case incorporates cost of iptacopan wastage, implemented in response to clarification question B15.

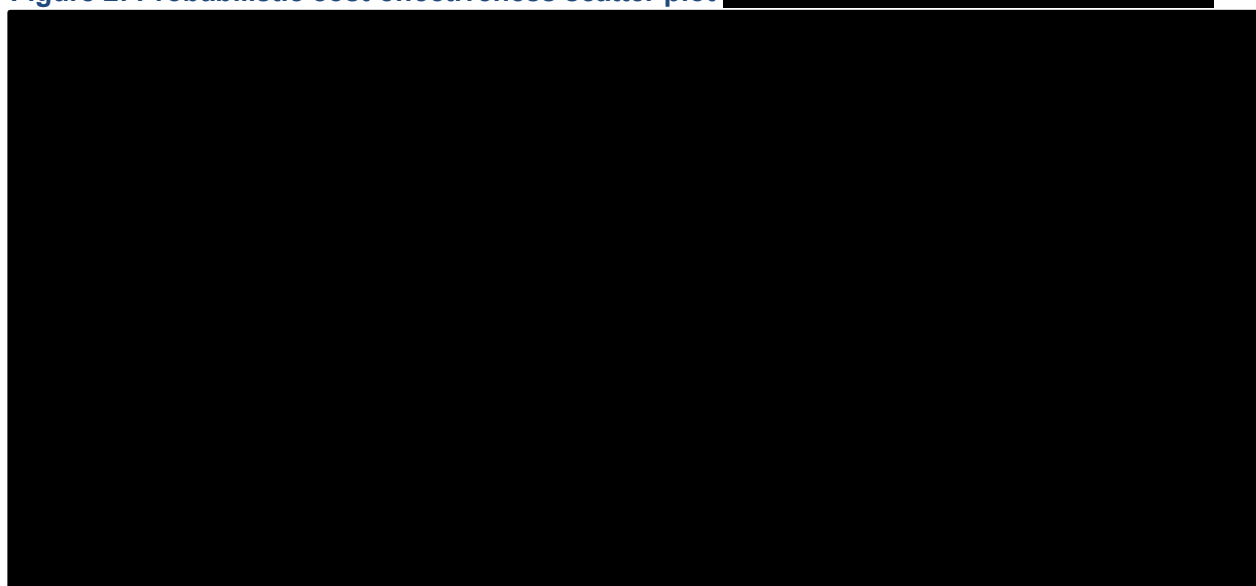
Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care.

Figure 1: Probabilistic ICER convergence plot



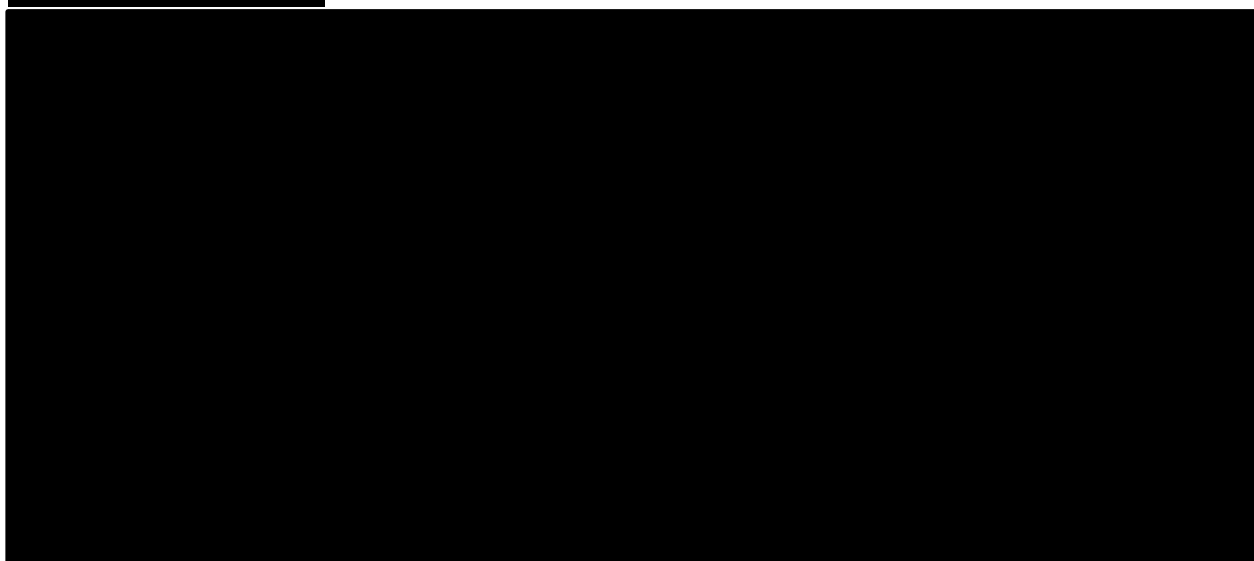
Abbreviations: ICER, incremental cost-effectiveness ratio; SOC, standard of care.

Figure 2: Probabilistic cost-effectiveness scatter plot



Abbreviations: QALY, quality-adjusted life year.

Figure 3: Cost-effectiveness acceptability curve from base-case PSA



Abbreviations: PSA, probabilistic sensitivity analysis; SoC, standard of care.

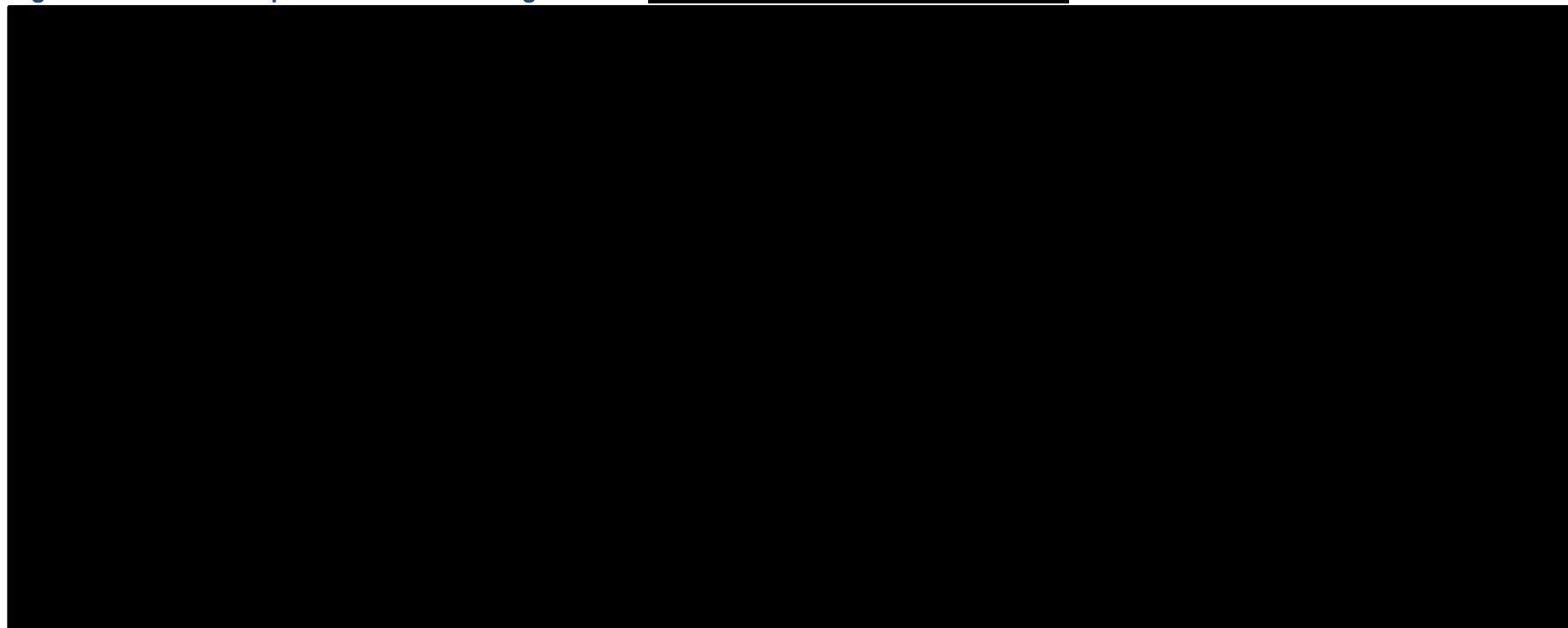
2.2.2 Deterministic sensitivity analysis

To further assess the robustness of the base-case model results, deterministic sensitivity analyses (DSA) were conducted by varying one model input at a time to assess which parameters had the largest impact on the ICER. Some parameters that do not have any uncertainty associated with the input value were excluded from the DSA.

For clinical and utility parameters, 95% CI were used, which were sourced from published data, where available, and calculated where data were not available. For other parameters, the variation was assumed to be a set percentage of the mean ($\pm 20\%$); upper and lower values were either calculated directly by adding or subtracting the respective percentage (for the cost inputs), or by using this to further calculate appropriate variations.

Results of the DSA show that the most influential parameter on the base-case ICER is the iptacopan treatment effect, with inputs relating to graft failure the next most influential parameters (Figure 4).

Figure 4: DSA tornado plot for absolute change in ICER [REDACTED]



Abbreviations: DSA, deterministic sensitivity analysis; eGFR, estimated glomerular filtration rate; HD, haemodialysis; HSUV, health-state utility value; ICER, incremental cost-effectiveness ratio; SoC, standard of care.

2.2.3 Scenario analysis

Scenario analyses were conducted to test the robustness of the model results to alternative model inputs and assumptions.

[REDACTED] with scenario analyses included in the company submission presented in Table 6 and scenario analyses conducted in response to requests from the EAG at clarification questions stage shown in Table 7.

Table 5: Results of deterministic scenario analyses included in the company submission

#	Scenario analysis description	Base case description	Incremental costs	Incremental QALYs	ICER	% ICER change from base case
-	Base case (deterministic)	-		1.74		N/A
Model settings						
1	CV events included	CV events not included		1.74		
Model inputs						
2	eGFR slope data from pooled population (APPEAR-C3G and Phase 2 native kidney cohort; up to 4.7 years iptacopan treatment duration)	eGFR slope data from APPEAR-C3G population (up to 2 years iptacopan treatment duration)		1.62		
3 ^a	eGFR slope data from APPEAR-C3G placebo comparison (based on 6 months of data)	eGFR slope data from APPEAR-C3G population (up to 2 years iptacopan treatment duration)		1.36		
4	Baseline characteristics and initial health state distribution from RaDaR	Baseline characteristics and initial health state distribution from APPEAR-C3G		1.66		
5	CKD stage transitions at upper eGFR bound of CKD stage	CKD stage transitions at midpoint of CKD stage, except for transition to KRT at KRT threshold		1.75		
6	Transplant eligibility of 93.18% for initial and 73.18% for subsequent transplants	Transplant eligibility of 83.2% for initial and subsequent transplants		1.73		
7	No maximum age for transplant	Maximum age for receipt of transplant 80 years		1.74		
8	Discontinuation of iptacopan, SGLT2i, MMF, CS upon entering CKD stage 5 (eGFR≤15 mL/min/1.73m ²)	Discontinuation of iptacopan, SGLT2i, MMF, CS upon reaching KRT threshold (eGFR ≤7.6 mL/min/1.73m ²)		1.72		
9	Mortality HRs based on Go et al. 2004	Mortality SMRs based on Wong et al. 2024		1.81		
10	CKD stage 1–4 utility values from Jesky et al. 2016	CKD stage 1–4 utility values from APPEAR-C3G		1.82		

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#	Scenario analysis description	Base case description	Incremental costs	Incremental QALYs	ICER	% ICER change from base case
11	Proportion of patients receiving SGLT2i assumed as 50%	Proportion of patients receiving SGLT2i based on APPEAR-C3G (5.4%)	██████	1.74	██████	██████
12	Healthcare resource use based on Kent et al. 2015; monitoring costs set to 0	Disease monitoring resource use based on UK advisory board survey	██████	1.74	██████	██████
13	Disease monitoring frequency based on NICE guideline NG203	Disease monitoring frequency based on UK advisory board survey	██████	1.74	██████	██████
14	KRT threshold of eGFR ≤10 mL/min/1.73m ²	KRT threshold of eGFR ≤7.6 mL/min/1.73m ²	██████	1.74	██████	██████
15	Iptacopan SAEs counted as 9 individual events in 189.9 patient years	Iptacopan SAEs counted as 5 episodes in 189.9 patient years	██████	1.74	██████	██████

Base case incorporates cost of iptacopan wastage, implemented in response to clarification question B15.

Footnotes: ^aScenario #3 should be interpreted with caution, since UK clinicians advised that predictions of SoC arm disease progression in this scenario lacked clinical validity (model-predicted median time to kidney failure with SoC 22.8 years, compared with approximately 10 years based on literature and advisors' clinical experience).

Abbreviations: CKD, chronic kidney disease; CS, corticosteroid; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; QALY, quality-adjust life year; RaDaR, National Registry of Rare Kidney Diseases; SAE, serious adverse event; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SMR, standardised mortality ratio.

Table 6: Results of deterministic scenario analyses requested by the EAG at clarification questions (CQ) stage ██████████

#	Scenario analysis description	Base case description	Incremental costs	Incremental QALYs	ICER	% ICER change from base case
-	Base case (deterministic)	-	██████	1.74	██████	N/A
Alternative KRT threshold values (CQ B3)						
16	KRT threshold of eGFR ≤5 mL/min/1.73m ²	KRT threshold of eGFR ≤7.6 mL/min/1.73m ²	██████	1.74	██████	██████
17	KRT threshold of eGFR ≤6 mL/min/1.73m ²		██████	1.74	██████	██████
18	KRT threshold of eGFR ≤7 mL/min/1.73m ²		██████	1.74	██████	██████

Alternative transplant eligibility inputs (CQ B4)						
19	Transplant eligibility of 63.89% for subsequent transplants	Transplant eligibility of 83.2% for initial and subsequent transplants	████████	1.85	████████	████████
20	Transplant eligibility of 0% for subsequent transplants (i.e. capped at maximum of 1 transplant)		████████	2.06	████████	████████
Alternative eGFR slope inputs (CQ B7)						
21	RaDaR data for SoC and iptacopan treatment effect from APPEAR-C3G (6-month double-blind period) (Analysis #4 in CEM)	eGFR slope data from APPEAR-C3G population (up to 2 years iptacopan treatment duration)	████████	1.16	████████	████████
22	Pre-iptacopan slope for SoC and iptacopan treatment effect from APPEAR-C3G (6-month double-blind period) (Analysis #5 in CEM)		████████	0.64	████████	████████
Iptacopan time to treatment discontinuation (TTD) using parametric survival extrapolations (CQ B8)						
Scenario analyses with TTD derived from pooled population (broad safety set)						
23	Exponential	Constant discontinuation, 1.57% probability per cycle	████████	1.75	████████	████████
24	Log-normal		████████	1.67	████████	████████
Scenario analyses with TTD derived from APPEAR-C3G population only						
25	Exponential	Constant discontinuation, 1.57% probability per cycle	████████	1.95	████████	████████
26	Log-normal		████████	1.69	████████	████████
Alternative AE incidence inputs (CQ B10)						
Broad safety set						
27	Scenario analysis I: All SAEs irrespective of suspected relationship with iptacopan and grade	Broad safety set: SAEs suspected to be related to iptacopan	████████	1.72	████████	████████
28	Scenario analysis II: All grade ≥3 AE (i.e. incidence >0%)		████████	1.73	████████	████████
29	Scenario analysis III: All grade ≥3 AE with an incidence of ≥5%		████████	1.74	████████	████████

30	Additional scenario analysis: All grade ≥3 AEs suspected to be related to iptacopan		████████	1.74	████████	████████
Controlled safety set						
31	Scenario analysis I: All SAEs irrespective of suspected relationship with iptacopan and grade	Broad safety set: SAEs suspected to be related to iptacopan	████████	1.74	████████	████████
32	Scenario analysis II: All grade ≥3 AE (i.e. incidence >0%)		████████	1.74	████████	████████
33	Scenario analysis III: All grade ≥3 AE with an incidence of ≥5%		████████	1.74	████████	████████
34	Additional scenario analysis: All grade ≥3 AEs suspected to be related to iptacopan		████████	1.74	████████	████████
Alternative post-transplant utilities (CQ B13)						
35	Liem et al. 2008 post-transplant utilities	Lee et al. 2005 post-transplant utilities	████████	1.49	████████	████████
Alternative AE disutilities (CQ B14)						
36	AE disutility value of 0.1	AE disutility value of 0.156	████████	1.74	████████	████████
37	AE disutility value of 0.2		████████	1.74	████████	████████
Alternative SAE cost (CQ B17)						
38	SAE cost £2,951.90	SAE cost £2,819.03	████████	1.74	████████	████████

Base case incorporates cost of iptacopan wastage, implemented in response to clarification question B15.

Abbreviations: AE, adverse event; CEM, cost-effectiveness model; CQ, clarification question; eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; KRT, kidney replacement therapy; QALY, quality-adjust life year; RaDaR, National Registry of Rare Kidney Diseases; SAE, serious adverse event; SoC, standard of care; TTD, time to treatment discontinuation.

2.3 Conclusions on cost-effectiveness

[REDACTED]

[REDACTED]

Given the current absence of effective disease-modifying treatment options for C3G, there remains a critical unmet need for targeted therapies in this ultra-rare disease. Individuals with C3G, carers, patient organisation representatives and clinicians have expressed a need for improved treatment options, given that current treatment with SoC does not prevent disease progression to kidney failure.¹⁻⁴ Iptacopan is therefore expected to provide a vital treatment option for people with C3G.

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Single technology appraisal

Iptacopan for treating complement 3 glomerulopathy [ID6283]

Summary of Information for Patients (SIP)

March 2025

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Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Iptacopan

Brand name: FABHALTA®

Please note: Cross-references to other sections or documents are highlighted in **orange**. Cross-references to figures and tables are highlighted in **teal**. Further explanations for the words and phrases in *italic text* are provided in the glossary (**Section 4b**).

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Iptacopan is expected to be used by adults with *complement 3 glomerulopathy (C3G)* in combination with another medicine called a *renin-angiotensin system (RAS) inhibitor*, or without a RAS inhibitor in adults who are unable to receive a RAS inhibitor.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The *Medicines and Healthcare products Regulatory Agency (MHRA)* is reviewing whether iptacopan should be granted a *marketing authorisation* as a treatment for adults with C3G. The anticipated date of MHRA approval is confidential. Iptacopan already has a marketing authorisation in another disease, a rare blood disease called paroxysmal nocturnal haemoglobinuria.¹

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Novartis collaborates with a range of stakeholders with an interest in C3G. This includes collaboration with patient groups to support improvements in health and care for individuals with C3G.

Novartis would like to disclose the following payments to patient groups:

- **Kidney Care UK**
 - 2024: £36,828.21 (£184.21 for healthcare professional (HCP) speaker/faculty travel; £1,644 for patient expert speaker and consultancy services; £20,000 for a grant; £15,000 sponsorship for improving healthcare)
 - 2025: £35,000 (grant to support Kidney Care UK's National Awareness Campaign)
- **Kidney Research UK**
 - 2024: £18,000 (for Novartis' membership in Kidney Research UK's industry partnership programme)
 - 2025: Novartis has agreed to make a payment of £51,000 (£18,000 for Novartis' membership in Kidney Research UK's industry partnership programme; £33,000 for sponsorship of a whitepaper on rare kidney diseases)
- **National Kidney Federation**
 - 2024: £8,000 (grant)

Transparency is important to Novartis and details of funding of patient groups across Novartis is disclosed on the Novartis website:

<https://www.novartis.com/investors/reporting-and-transparency-hub/patient-organization-funding>

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is C3G?

C3G is a very rare kidney disease that is chronic (lifelong) and progresses (worsens) over time. The disease commonly affects young people. The average age at diagnosis is 21–23 years old.²⁻⁴

C3G severely damages the kidneys,⁵ which can cause many different problems. As C3G gets worse over time, the kidneys may stop working ('kidney failure'), meaning they can no longer remove waste and extra water from the blood.

What causes C3G?

C3G is caused by a part of the *immune system*, called the *complement system*, working incorrectly. The complement system helps to fight bacteria and viruses.⁶ However, in C3G, the complement system is too active because of a person's genes or problems that develop during a person's life.⁶

Due to the complement system not working correctly, a specific protein called *complement component 3 (C3)* is broken down into small pieces (fragments).⁶ These fragments of C3 become lodged in the kidney, causing inflammation (an immune system response) and damage to the kidney's filtering units (*glomeruli*).⁶ Damaged glomeruli are not able to filter the blood very well, and waste products build up in the blood causing more kidney damage.⁶

How many people have C3G?

C3G is a very rare disease. Therefore, it is difficult to determine the exact number of people with C3G. It is estimated that there are approximately 427 people in England living with C3G.^{5, 7-9}

What are the signs and symptoms of C3G?

Individuals with C3G can have a variety of signs and symptoms. These include too much protein in the urine (*proteinuria*), blood in the urine (haematuria), high blood pressure (hypertension), tiredness (fatigue), and swelling of the hands, feet and ankles (oedema). These can cause foamy urine, less urine production, headaches, and joint pain.^{10, 11}

How does C3G progress over time?

As C3G gets more severe, symptoms get worse, and complications increase. This can include worsening fatigue, and the development of high blood pressure and cardiovascular disease (conditions affecting the heart or blood vessels).^{2, 12, 13}

Approximately half of individuals with C3G have kidney failure within 10 years of diagnosis.^{3, 5, 14, 15} People who have kidney failure will require *kidney replacement therapy*. There are two options:¹⁶

- *Kidney transplant* – a healthy kidney from a donor is placed into the body using surgery, to take over the function of the kidneys which stopped working
- *Dialysis* – a treatment, often with a machine, that removes waste and excess fluid from the blood when the kidneys are not functioning

Kidney transplants do not address the cause of C3G so the disease can return following a transplant of a new kidney.¹⁷ If the disease returns and the transplanted kidney stops working (graft failure), the person will need to receive another transplant or go back to receiving dialysis.

How is C3G progression measured?

Proteinuria is when there is too much protein in the urine. This indicates that the kidneys are not working properly. In C3G, the amount of protein in the urine can be used to assess

how well the kidneys are functioning by measuring the *urine protein-to-creatinine ratio (UPCR)*. UPCR is a test that compares the amount of protein and a waste product called *creatinine* in a urine sample. In people with no kidney disease, the kidneys filter blood effectively, without letting significant amounts of protein pass into the urine. In people with C3G, UPCR levels are increased, which is a sign of worse kidney function.^{5, 18-21}

The *estimated glomerular filtration rate (eGFR)* measures how well the kidneys are filtering waste from the blood. eGFR is measured using a blood test. In people with C3G, eGFR levels are lower than normal, which is a sign of worse kidney function.^{5, 21, 22}

To categorise how well people's kidneys are working and measure whether a person's C3G is getting worse, a system called Chronic Kidney Disease (CKD) staging is used.¹⁹ There are 6 stages (CKD stage 1, 2, 3a, 3b, 4 and 5) based on eGFR levels, with Stage 1 being the mildest and Stage 5 indicating kidney failure.¹⁹

Impact of C3G on quality of life

The wide-ranging symptoms of C3G can have a negative impact on a person's quality of life. This can include:

- Swelling of hands, feet and ankles can cause difficulties with standing, walking and climbing stairs.^{23, 24}
- Severe fatigue can limit social activities and cause individuals to need to sleep during the day and feel too tired to eat.²⁵
- Episodes of gout (severe pain and joint swelling) may limit physical activities.^{11, 23}

The symptoms of C3G, restrictions to lifestyle and diet, and kidney replacement therapies all impact the quality of life of individuals with C3G (see **Section 2d** for more information). People with C3G face uncertainty around disease progression and the lack of available treatment options, which can impact their mental health and lead to anxiety and depression.^{23, 26} C3G is a very rare disease, with limited information available and this can also cause feelings of helplessness, isolation and loneliness.^{23, 26}

C3G can impact the ability of people to attend education and work regularly, potentially limiting their future career opportunities.²⁶ C3G also impacts the families and carers of people with C3G. Carers may be required to support with day-to-day activities and attending medical appointments. This can impact the carer's ability to work or study (productivity), adding an economic burden.

As mentioned, approximately half of people with C3G progress to kidney failure within 10 years of diagnosis and then require kidney replacement therapies.^{3, 5, 14, 15} Kidney replacement therapies can also have negative impacts on people with C3G. People with C3G have to wait on average 2–3 years for a suitable donor organ and may require dialysis whilst they wait.²⁷ Transplants are associated with multiple risks including the risk of surgery, infections, kidney rejection (where the body sees the transplanted kidney as a threat and attacks it) and graft failure (where the transplanted kidney stops working).²⁸ To prevent kidney rejection, medicines called *immunosuppressants* are used to stop the immune system from attacking the transplanted kidney. These medicines are also associated with *side effects*, including increased risk of infections, high blood pressure,

weight gain, difficulty sleeping, and gastrointestinal side effects, which can all impact quality of life, as well as an increased risk of cancer associated with long-term use.²⁹

Dialysis treatment is repeated for the rest of a person's life or until the person receives a kidney transplant. There are two types of dialysis. One is carried out at a clinic three times a week to filter the blood through a machine and takes four hours per session.³⁰

Alternatively, dialysis can be done at home but this usually needs to be repeated every day.³⁰ Therefore, dialysis requires people with C3G to take time out of work, education or social activities, which reduces quality of life.^{23, 26} People who have dialysis can experience side effects of fatigue, low blood pressure, itchy skin, joint pain and muscle cramps.³¹

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

People with C3G go to the doctor when they have symptoms such as blood in the urine, foamy urine (a sign of too much protein in the urine), fatigue, or swelling in the hands and feet.⁶ If a doctor suspects that someone has a kidney disease like C3G, they will test the person's blood and urine to measure how well the kidneys are working.

To diagnose C3G, a kidney biopsy is needed. The kidney biopsy involves inserting a needle through the skin that lies over the kidney to remove a small piece of tissue from the kidney, which is then looked at with special microscopes to check for signs of C3G.³²

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There are currently no treatments that directly target the cause of C3G.¹⁹ The current treatment options (referred to as standard of care) are used for many different diseases and aim to slow down the process of kidney damage and manage symptoms. Standard of care can include the following treatments:^{6, 19}

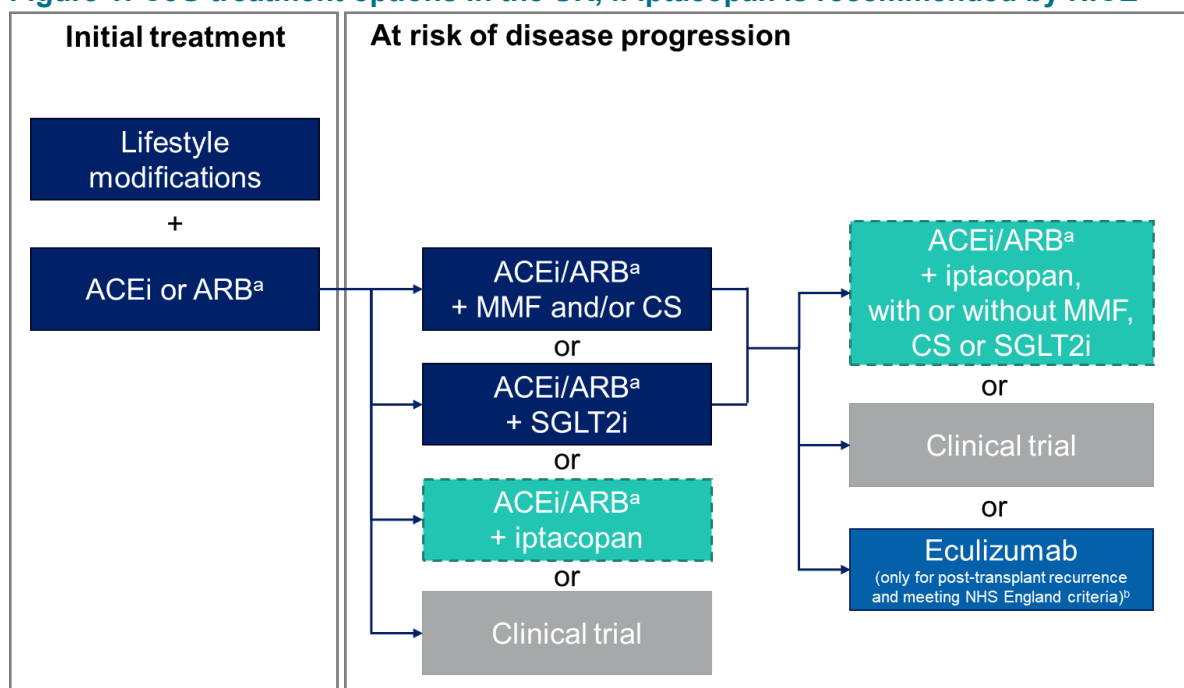
- Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) – these are used to reduce protein in the urine and to lower blood pressure. ACEi/ARB are examples of a type of treatment called RAS inhibitors.

- Corticosteroids (CS) and/or mycophenolate mofetil (MMF) – these are examples of immunosuppressants and are used to reduce inflammation.
- Sodium-glucose co-transporter 2 inhibitors (SGLT2i) – these are used to lower blood pressure in the kidneys.
- Eculizumab – this targets a part of the complement system. Only a very limited number of people whose C3G has returned after a kidney transplant and meet a list of criteria can receive this treatment in the UK.
- *Clinical trial* enrolment – individuals whose disease continues to worsen with standard of care treatments are often considered for a clinical trial where a new medication is tested, if available.

How the currently available treatments are used is shown in **Figure 1**.

Figure 1 also shows when iptacopan could be used, if it is recommended by NICE. Adults with C3G are expected to receive iptacopan if treatment with an ACEi or ARB alone is not sufficient to reduce the risk of disease progression. Iptacopan would be given in addition to an ACEi or ARB, unless the person is unable to receive ACEi/ARB. Iptacopan may also be given to individuals who are receiving MMF, CS or SGLT2i.

Figure 1: C3G treatment options in the UK, if iptacopan is recommended by NICE



Footnotes: ^aTo a maximally tolerated licensed dose, unless intolerant or contraindicated. ^bOnly a very small number of patients with highly aggressive post-transplant recurrence of C3G qualify for treatment with eculizumab under the NHS England criteria.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CS, corticosteroids; MMF, mycophenolate mofetil; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SGLT2i, sodium-glucose co-transporter 2 inhibitor

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what

matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

As discussed in **Section 2a**, C3G can have a negative impact on a person's quality of life. The symptoms of C3G and, after kidney failure, the requirement for dialysis can make it difficult to carry out daily activities, socialise, exercise and work.

A survey of people with C3G was conducted using a questionnaire called the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue). This questionnaire measures how fatigue affects people's daily activities and their overall quality of life.³³ The questionnaire found that 78% of people with C3G limit their social activities due to fatigue, 77% need to sleep during the day and 47% feel too tired to eat.³³ In a 2018 forum for people with C3G and their carers (conducted by the National Kidney Foundation in the United States), people with C3G expressed that "the fatigue is overwhelming", impacting all aspects of their lives.²³

C3G can also have an impact on a person's mental health.²³ People with C3G discussed feeling scared and lonely, with their future unknown. Some people with C3G noted:²³

- "What's most difficult is knowing that time is not on my side...without a viable drug treatment, I know that a healthy diet, exercise, and following doctor's orders will not stop the progression of this disease...This absolutely frightens me...I can only imagine things getting worse"
- "You feel like you're going through it alone"

As mentioned in **Section 2a**, people with C3G often feel helpless and isolated as there is not much information available on this rare disease. They can also experience anxiety and depression as they worry about their symptoms and disease progression.^{23, 26}

As mentioned in **Section 2a**, approximately half of people with C3G progress to kidney failure within 10 years of diagnosis.^{3, 5, 14, 15} Kidney replacement therapies can increase the disease burden for people with C3G. Dialysis is a very time-consuming treatment which puts a burden on the daily life of people with C3G and their carers. A UK patient organisation reported how individuals with C3G have to "fit a life around dialysis treatment", with in-centre dialysis "tak[ing] out three days a week of normal life", once transport time, waiting time, and the four-hour dialysis duration are taken into account.³⁴ Young people with C3G have reported not being able to attend education regularly, which can impact their social lives and future careers.^{23, 26}

The burden of C3G is increased for some individuals due to the pressure of making treatment decisions, specifically when it comes to the choice of receiving a transplant, knowing that C3G can return in the transplanted kidney. People with C3G expressed feeling that they must "trade in their current conditions for another unknown."²³ This burden increases with continued disease progression.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

As mentioned in **Section 2a**, C3G is caused by the incorrect functioning of a part of the immune system called the complement system. Iptacopan is a treatment which directly targets the cause of C3G in the complement system. Iptacopan reduces the amount of C3 in the kidneys, slowing down kidney damage.^{33, 35}

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

As mentioned in **Section 1b**, iptacopan is expected to be used in combination with a RAS inhibitor, or without a RAS inhibitor in adults who are unable to receive a RAS inhibitor. People who take iptacopan may also continue to take other treatments such as SGLT2i, CS, MMF.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Iptacopan is taken twice daily as a 200 mg capsule that is swallowed.³⁶ Iptacopan has no special storage conditions, so it does not need to be kept in the fridge.³⁶ C3G is a chronic disease and treatment may be lifelong.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size,

comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The main clinical trial for iptacopan in C3G is called the APPEAR-C3G study.³⁷ Additional information is available from an earlier trial (a *Phase 2 trial*) and an ongoing extension study, where people who participated in the other two trials can continue to receive iptacopan.

APPEAR-C3G was a *Phase 3 trial*, which assessed how well iptacopan works to treat C3G (its *efficacy*) and how safe the medicine is. In the trial, iptacopan was compared to *placebo* (a treatment that looks the same as the treatment being tested but has no active medicine). A comparison with placebo is used to understand if the real treatment being tested works better than no treatment. Participants were randomly assigned to take either iptacopan or placebo for six months (the *double-blind* period, where participants and researchers do not know what treatment each participant is receiving).³⁷ Afterwards, participants started the *open-label* period (where the participants and researchers know which treatment is being given to each participant), which also lasted six months and where everyone received iptacopan. Participants who started the double-blind period on iptacopan continued taking iptacopan for the open-label period. Participants who started the double-blind period on placebo switched to iptacopan for the open-label period.³⁷

The Phase 2 study provides data on individuals who have not had a kidney transplant as well as individuals who received iptacopan after C3G had returned in their kidney transplant (individuals with a transplant were not included in APPEAR-C3G).³⁵ The Phase 2 study consisted of 12 weeks of treatment with iptacopan.³⁵

After completing APPEAR-C3G or the Phase 2 study, participants could enter the extension study where they continued iptacopan treatment.³⁸ This study provides data on the long-term safety and efficacy of iptacopan.

Table 1 summarises information on these three clinical trials. Further information can be found on the ClinicalTrials.gov website (www.clinicaltrials.gov) and searching for the relevant trial ID; for example, NCT04817618 for APPEAR-C3G.

Table 1: Clinical trials investigating iptacopan for C3G

Trial name and number	APPEAR-C3G (Phase 3; NCT04817618) ³⁷	Phase 2 trial (NCT03832114) ³⁹	Extension study (NCT03955445) ³⁸
Location	International (including hospitals in the UK)		
Number of participants included	74	27	92
Population (who could participate in the trial)	People aged 12–60 years with C3G who have not had a kidney transplant	People aged 18 years or older with C3G who have either: not had a kidney transplant, or have had a kidney transplant but their C3G has returned	People who completed the APPEAR-C3G study or the Phase 2 study

Treatment being tested	Iptacopan in combination with an ACEi or ARB. People who were receiving CS, MMF or SGLT2i before the trial, also continued taking this medicine during the trial		
Comparator	Placebo	Not applicable (no comparator arm)	Not applicable (no comparator arm)
Completion date	Complete for adult participants (people aged 18–60 years). The study is still ongoing for adolescents (people aged 12–17 years) and expected to complete in 2026	Complete	The trial is expected to complete in 2033

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C3G, complement 3 glomerulopathy; CS, corticosteroids; MMF, mycophenolate mofetil; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Sources: ClinicalTrials.gov (NCT04817618);³⁷ ClinicalTrials.gov (NCT03832114);³⁹ ClinicalTrials.gov (NCT03955445).³⁸

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The APPEAR-C3G trial described in **Section 3d** above studied the efficacy (how well a treatment works) and safety (side effects) of iptacopan as a treatment for C3G. This was compared with placebo.³⁷ The efficacy of iptacopan was assessed by measuring the change in UPCR and change in eGFR in people treated with iptacopan or placebo (described in **Section 2a**).

After six months of treatment in the APPEAR-C3G trial, individuals taking iptacopan had *clinically meaningful* and *statistically significantly* lower UPCR levels, compared to those taking placebo.^{33, 40} Individuals taking iptacopan for six months in the APPEAR-C3G trial also had an improvement in eGFR while patients taking placebo had a decline, suggesting that with iptacopan the disease worsens at a slower speed. However, this result was not statistically significant and is therefore uncertain. Data from participants who received iptacopan for 12 months (in the APPEAR-C3G trial) or longer (in the extension study) show that the effects of iptacopan are maintained with longer-term treatment.

More results on the efficacy of iptacopan can be found in **Section 2 of the company submission**.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The 'EQ-5D' is a questionnaire that is recommended by NICE for measuring a person's quality of life. As the EQ-5D is a general tool used for all diseases, it does not always capture the specific challenges associated with a disease. In the APPEAR-C3G trial, people with C3G were asked to answer questions about their quality of life, using EQ-5D.^{33, 40} Further information about the EQ-5D data is provided in **Section 3i**.

The 'FACIT-Fatigue' is a questionnaire to understand how fatigue affects daily activities and the overall quality of life of individuals.⁴¹ Fatigue is a common symptom for people with C3G.⁴² However, the participants of the APPEAR-C3G study did not have more fatigue than people without C3G. This was likely because most individuals were in an early stage of disease. In APPEAR-C3G, FACIT-Fatigue was measured before and during the trial. There was no statistically significant change in FACIT-Fatigue scores for individuals treated with iptacopan.^{33, 40}

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has the potential to result in side effects, and the same medicine can produce different reactions in different people. Across the three trials, iptacopan was generally well *tolerated* (participants were able to put up with the side effects of their treatment) and most side effects were mild or moderate.

The most common side effect occurring in people treated with iptacopan across all three trials was COVID-19, which occurred in 29.7% of people. The trials were conducted during the COVID-19 pandemic. This likely contributed to the high number of people with COVID-19. The other most common side effects were nasopharyngitis (13.9%; the common cold), increased levels of a protein called creatine phosphokinase in the blood (10.9%), headache (8.9%), cough (7.9%), anaemia (5.9%; fewer red blood cells than normal) and upper respiratory tract infections (5.9%; infections affecting the nose, throat, and airways).

19.8% of people treated with iptacopan experienced serious side effects. The most common serious side effects were infections. There were 3 individuals who stopped taking iptacopan due to serious side effects during the extension study. But these side effects were considered not related to iptacopan by the participants' doctors. There was one death across the three studies, which the participant's doctor did not consider to be caused by iptacopan.

Because of the way iptacopan works on the immune system, there is an increased risk of infections. To reduce the risk of serious infections, people are required to have several vaccinations before starting iptacopan.³⁶

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There is a high unmet need in C3G, with no treatments available that directly target the disease. With current treatments, approximately half of the people with C3G need dialysis or a kidney transplant within 10 years after diagnosis.

Iptacopan is expected to be the first treatment that targets the cause of C3G. In the main clinical trial, iptacopan reduced proteinuria more than placebo. Clinical trial data also suggest that with iptacopan, the disease may progress at a slower speed. Therefore, iptacopan is expected to improve symptoms and quality of life, and fewer people with C3G may need dialysis or a kidney transplant in the future. Treatment with iptacopan was also well tolerated in the clinical trials.

Iptacopan is a capsule which can be swallowed at home twice a day.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Like all medications, iptacopan can cause side effects. However, in the clinical trials most side effects were mild or moderate. The main side effects associated with iptacopan are listed in **Section 3g**. Some people treated with iptacopan had serious infections. To reduce the risk of serious infections, people are required to have several vaccinations before starting iptacopan.³⁶

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

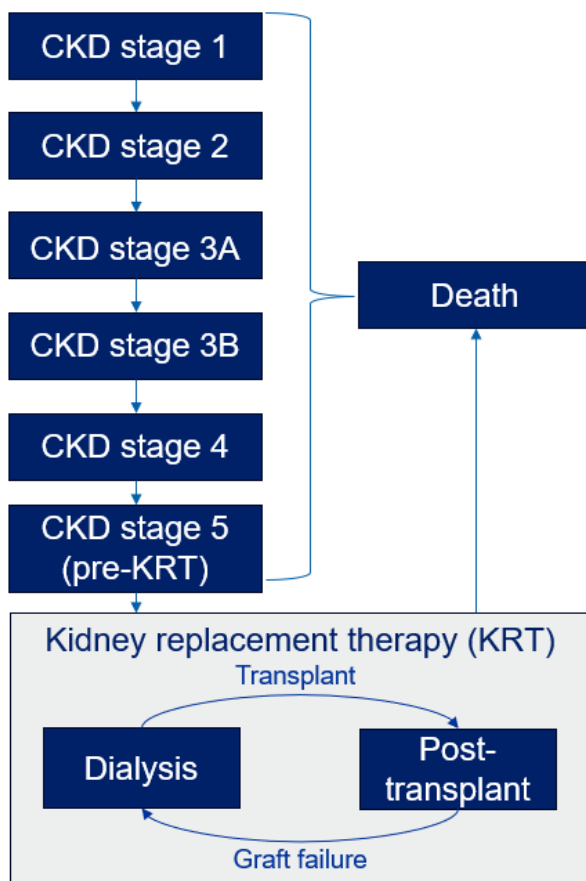
The pharmaceutical company used a health economic model to compare the costs and benefits of iptacopan with the costs and benefits of the currently used treatments for C3G (standard of care). The health economic model will help NICE decide if the NHS should pay for iptacopan as a treatment for C3G.

How the economic model reflects C3G

A picture of the economic model is shown below (**Figure 2**). To model the worsening of C3G over the duration of a person's life, the disease course was split into different stages, known as 'health states.' The model uses CKD stages 1–5 (described in **Section 2a**) to define these health states, and also includes health states for dialysis, kidney transplant and death.

At the start of the model, people with C3G are in CKD stages 1–4. Over time, if their disease worsens, they move to worse CKD stages. People whose kidneys have stopped working are then modelled to receive dialysis or a transplant. The model also takes into account that C3G can return in some people who have received a transplant. If the transplanted kidney stops working (graft failure), the model considers that this person will then need dialysis or another transplant.

Figure 2: Economic model



Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy.

The different health states of the economic model are associated with different costs, such as costs of visiting a doctor, costs of dialysis or a transplant, and medication costs. The different health states are also associated with different health outcomes. For example, people receiving dialysis may have a worse quality of life and a shorter life expectancy than people in earlier CKD stages.^{7, 43} All costs and health outcomes that occur over a person's lifetime are included in the calculations of the economic model.

Modelling the effectiveness and safety of iptacopan

All calculations in the model are done twice:

- once for a hypothetical group of adults with C3G who receive current standard of care, and
- once for a hypothetical group of adults with C3G who receive iptacopan.

Based on the results from the APPEAR-C3G trial (see [Section 3e](#)), people treated with iptacopan may experience a slower disease progression (less eGFR decline) than people treated with standard of care. Therefore, people in the model who are treated with iptacopan are less likely to move to worse CKD stages, and fewer people in this group need dialysis or a transplant.

The economic model also uses data from the clinical trials on the number of people who had serious side effects with iptacopan, and the number of people who stopped iptacopan treatment (e.g. due to side effects or no longer wanting to take it).

Modelling other important data in C3G

Some information was not available from the clinical trials and had to be taken from other sources. This includes information on how many people receive a transplant or different types of dialysis, and how quickly a transplanted kidney can stop working (graft failure). This information was provided by the National Registry of Rare Kidney Diseases (RaDaR), which collects data from people with C3G who live in the UK and have agreed that their information is included in this database.⁹

No information was available on the risk of death in people with C3G. Instead, data was used from a broader group of people with various rare kidney diseases.⁷

Modelling how much iptacopan improves quality of life

Participants of the APPEAR-C3G trial completed the EQ-5D questionnaire (described in **Section 3f**) which provided information on their quality of life. The responses to this questionnaire were used to calculate quality of life scores (*utility values*) which were used in the economic model. Since APPEAR-C3G did not include people in CKD stage 5 or who were on dialysis or transplanted, information for these groups was taken from published studies which reported quality of life in people with other chronic kidney diseases.^{44, 45} These utility values show that people in earlier CKD stages have better quality of life than people in later CKD stages or on dialysis.

With people receiving iptacopan staying in earlier CKD stages for longer, the group of people receiving iptacopan in the economic model therefore have overall better quality of life than the group of people receiving standard of care.

Modelling how NHS costs differ with iptacopan

Various NHS costs were included in the economic model, including:

- The cost of iptacopan
- The cost of standard of care medications
- The cost of people with C3G seeing their doctor
- The cost of regular urine and blood tests
- The cost of kidney transplants and dialysis, including the cost of transport to and from dialysis centres
- The costs of treating the side effects of iptacopan treatment
- The cost of vaccinations that people must receive before starting iptacopan (see **Section 3g**)

In the economic model, the hypothetical group of people receiving iptacopan has lower costs for dialysis and transplants. However, the medication costs for the iptacopan group are higher because of the additional cost of iptacopan.

The results of the economic model

The economic model calculates the average total costs and average total health outcomes for a hypothetical group of adults with C3G receiving current standard of care, and for a hypothetical group of adults with C3G receiving iptacopan. The total costs and total health outcomes of these two groups are then compared to calculate the differences. When doing these calculations, health outcomes are expressed using a measure called quality-adjusted life years (QALYs), which considers how long people live and their quality of life.

Based on the calculations of the pharmaceutical company, treatment with iptacopan is associated with more costs and more health benefits (more QALYs) than current standard of care. This means that whilst iptacopan costs more on average to the NHS, those people treated with iptacopan are expected to have improved quality of life and may live longer than people treated with current standard of care.

NICE will need to decide whether this expected improvement in quality and length of life is worth the additional costs.

Uncertainty

This is the first time that NICE assesses a treatment for C3G. Therefore, there is no experience with economic models for C3G.

All economic models are associated with some uncertainty because their development involves using data from many different sources and making assumptions. The pharmaceutical company has tried to reduce this uncertainty by getting advice from UK clinicians who have a lot of experience in treating people with C3G in the NHS. Where possible, data sources used are from the UK and provide information on people with C3G specifically.

Because C3G is a very rare disease, it is more difficult to do clinical trials. Therefore, the number of people in the iptacopan clinical trials was smaller than it tends to be for more common diseases. The pharmaceutical company asks the NICE Committee to take into account that C3G is a very rare disease, when they assess iptacopan as a potential treatment for C3G.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

With currently used treatments, about half of the people with C3G need dialysis or a kidney transplant within 10 years of diagnosis. Iptacopan is expected to be the first treatment which directly targets the cause of C3G. Therefore, the pharmaceutical

company considers that iptacopan is an innovative treatment which may provide significant additional benefit for people with C3G, compared with current treatments.

Because of the way calculations are done in economic models, it is possible that not all benefits of iptacopan have been included ('benefits not captured in the QALY'). The EQ-5D questionnaire may not capture the full impact of C3G on the quality of life of individuals with C3G and their families and carers, including the feelings of helplessness, isolation and loneliness.^{23, 26}

In addition, the economic model does not consider the impact of dialysis on the time and productivity of people with C3G and their carers, who may have to reduce their hours at work or in education.^{23, 46} By fewer people requiring dialysis with iptacopan, the burden would be reduced for individuals with C3G and their carers, but also for the NHS.

By fewer people with C3G requiring a kidney transplant with iptacopan, the NHS transplant waiting list could become shorter and people with other kidney diseases who need a transplant may be able to get this more quickly. These additional benefits of iptacopan are not captured in the economic model results. However, the pharmaceutical company asks NICE to take these factors into consideration when assessing iptacopan.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

[Find more general information about the Equality Act and equalities issues here](#)

At the moment, clinical trial results for iptacopan in C3G are only available for adults. Therefore, the expected marketing authorisation and this NICE assessment will only cover adults with C3G. However, the pharmaceutical company aims to make iptacopan available also to younger people with C3G as soon as possible.

Research in the UK has identified that there is inequality across ethnic groups in the treatment of kidney disease. Individuals of Black and Asian descent are more likely to have kidney failure faster and wait longer for transplants than White people.^{27, 47} Iptacopan reduces disease progression and therefore the need for dialysis or a transplant and so has the potential to address this inequality.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Further information on C3G:

- [C3 glomerulopathy \(C3G\) | Kidney Care UK](#)
- [MPGN/DDD Support Group](#)
- [MPGN, DDD & C3 Glomerulopathy | UK Kidney Association](#)

Further information on iptacopan clinical trials:

- <https://clinicaltrials.gov/study/NCT04817618>
- <https://clinicaltrials.gov/study/NCT03832114>
- <https://clinicaltrials.gov/study/NCT03955445>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Clinically meaningful	An outcome that has a significant impact on someone's health, treatment decisions or quality of life, as agreed by experts in the disease area
Clinical trial	A type of research study that tests how well new medical approaches (like a new medicine) work in people. Also called a clinical study
Complement 3 glomerulopathy	A rare kidney disease resulting in the build-up of a protein called complement component C3 in the kidneys. This can lead to inflammation and damage to the kidneys

Complement component 3 (C3)	A protein in the blood that plays a key role in the body's immune system, helping to fight infections. When the body responds to a threat, C3 is activated, which can sometimes lead to inflammation
Complement system	A group of proteins that is part of the immune system and helps fight infections and clear away damaged cells
Creatinine	A waste product in the blood that gets removed by the kidneys
Dialysis	A treatment to remove waste and excess fluid from the blood
Double-blind	A type of clinical trial design where participants and researchers do not know what treatment each participant is receiving
Efficacy	The ability of a medicine to produce a desired positive effect on a disease or illness in a clinical trial
Estimated glomerular filtration rate (eGFR)	A test that checks how well the kidneys are filtering waste from the blood. It helps detect kidney problems early and monitor their progression
Glomeruli	Filters in the kidneys that remove waste and extra fluids from the blood
Immunosuppressant	A medication used to weaken the body's immune system
Immune system	A complex network of cells, tissues, organs and the substances they make, that help the body fight infections and other diseases
Kidney replacement therapy	This treatment helps perform the function of the kidneys when they are no longer working properly. It includes options like dialysis and kidney transplant
Kidney transplant	A surgical procedure where a healthy kidney from a donor is placed into the body to take over the function of kidneys which are no longer working
Marketing authorisation	A licence provided by a regulatory body that allows a medicine to be given to people in a particular country
Medicines and Healthcare products Regulatory Agency (MHRA)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom
Open-label	A type of clinical trial design where both the participants and researchers know which treatment is being given to each participant
Phase 2	These trials test a new treatment on a group of people with the disease. This trial phase helps determine the right dosage and gathers more information on potential side effects
Phase 3	These trials test the efficacy and safety of a new treatment in a larger group of people with the disease. The new treatment is often compared with another treatment or placebo
Placebo	A treatment that looks the same as the treatment being tested but has no active medicine. It is often used in double-blind clinical trials to understand if the real treatment being tested works better than no treatment
Proteinuria	A condition where there is too much protein in the urine. It often indicates that the kidneys are not working properly
Renin-angiotensin system (RAS) inhibitors	Medications that block the renin-angiotensin system (RAS), which regulates blood pressure and fluid balance. These drugs help lower blood pressure, protect the kidneys, and reduce the risk of heart disease. Examples include angiotensin converting

	enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB)
Side effects	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe
Statistically significant	A result in data analysis that is unlikely to have occurred by chance, indicating a high likelihood that the observed effect is real, based on a predefined threshold
Tolerated	A patient's ability to put up with the side effects of treatment
Urine protein-to-creatinine ratio (UPCR)	A test that compares the amount of protein and a waste product called creatinine in a urine sample. This test helps determine the level of proteinuria and, by extension, the condition of the kidneys
Utility value	A number which expresses quality of life and is used in economic models. It is generally a number between 0 (representing death) and 1 (perfect health)

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal Iptacopan for treating complement 3 glomerulopathy [ID6283]

Clarification questions

April 2025

File name	Version	Contains confidential information	Date
ID6283_Iptacopan for C3G_Clarification questions response_25Apr25_[REDACTED]	1.0	Redacted	25 th April 2025

Section A: Clarification on effectiveness data

Literature searches

A 1. There appear to have been transcription errors in some of the Cochrane Library search strategies.

Please resubmit the following lines of the Cochrane Library search strategies:

- Appendix B; Table 4: #9
- Appendix F; Table 4: #9, #21, #35, #46
- Appendix G; Table 4: #51

We apologise for transcription errors in the Cochrane Library search strategies as originally presented. The correct search strategy tables are provided below, with updated parts underlined and highlighted in green. In the Appendix F table, please note that a row was originally missed and has now been included as row 21, with the numbering of rows 22–35 (formerly 21–34) updated, hence highlighted green. The former row 35 was a transcription error and not part of the search strategy, so has now been removed. We confirm that these were transcription errors only, and the number of final hits as presented in the originally submitted tables is correct.

Table 1. Corrected version of Appendix B; Table 4: Search terms used in the Cochrane Library (via the Ovid SP platform)

Term group	#	Searches	Original SLR (03.10.2021)	SLR update (14.10.2024)
C3 Glomerulopathy	1.	MeSH descriptor: [Glomerulonephritis] explode all trees	933	1,323
	2.	MeSH descriptor: [Glomerulonephritis, Membranoproliferative] explode all trees	20	28
	3.	MeSH descriptor: [Complement C3] explode all trees	289	339
	4.	(#1 OR #2) AND #3 (Word variations have been searched)	16	18
	5.	("c3 glomerulopathy" or C3G or "dense deposit disease" or "dense-deposit-disease" or "dense deposit-disease" or "dense-deposit disease" or "c3 glomerulonephritis" or C3GN or "Complement component 3 glomerulopathy" or "Complement-component 3 glomerulopathy" or "Complement component-3 glomerulopathy" or "Complement-component-3 glomerulopathy" or "complement 3 glomerulopathy" or "complement-3 glomerulopathy"):ti,ab,kw (Word variations have been searched)	28	70

Term group	#	Searches	Original SLR (03.10.2021)	SLR update (14.10.2024)
	6.	(((((dense NEAR/2 deposit NEAR/2 disease) OR (c3 NEAR/2 glomerulo*) OR (complement NEAR/2 glomerulo*) OR (complement-3 NEAR/2 glomerulo*) OR ("complement 3" NEAR/2 glomerulo*) OR ("component 3" NEAR/2 glomerulo*) OR ("component-3" NEAR/2 glomerulo* OR (component NEAR/2 glomerulo*))))):ti,ab,kw (Word variations have been searched)	17	54
	7.	((("membranoproliferative glomerulonephritis" NEAR/2 "type ii" OR "membranoproliferative glomerulonephritis" NEAR/2 "type 2" OR "mesangiocapillary glomerulonephritis" NEAR/2 "type ii" OR "mesangiocapillary glomerulonephritis" NEAR/2 "type 2")):ti,ab,kw (Word variations have been searched)	1	1
	8.	((("type ii" NEAR/2 mpgn OR "mpgn" NEAR/2 ii OR "ddd" NEAR/2 "mpgn ii" OR "type 2" NEAR/2 mpgn OR "mpgn 2" OR ddd NEAR/2 "mpgn 2")):ti,ab,kw (Word variations have been searched)	2	3
	9.	OR #4-#8 (Word variations have been searched)	45	88
Final Hits (original SLR)	10.	#9 in Cochrane Reviews and Trials (Word variations have been searched)	45	88
Final hits (SLR update)	11.	#9 with Cochrane Library publication date from Oct 2021 to present, in Cochrane Reviews and Trials	NA	42

Databases searched: The Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials).

Abbreviations: SLR: systematic literature review.

Table 2. Corrected version of Appendix F; Table 4: Search strategy for the Cochrane Library for the original and update HRQoL SLRs (CDSR/CENTRAL, via Cochrane Library interface)

Term group	#	Search Term	Original SLR (22.01.2021)	Update SLR (12.11.2024)
Disease	1.	MeSH descriptor: [Glomerulonephritis] explode all trees	910	1,326
	2.	MeSH descriptor: [Glomerulonephritis, Membranoproliferative] explode all trees	20	28
	3.	MeSH descriptor: [Complement C3] explode all trees	286	339
	4.	(#1 OR #2) AND #3 (Word variations have been searched)	16	18
	5.	("c3 glomerulopathy" OR C3G OR "dense deposit disease" OR "dense-deposit- disease" OR "dense deposit-disease" OR "dense-deposit disease" OR "c3 glomerulonephritis" OR C3GN OR "Complement component 3	22	71

Term group	#	Search Term	Original SLR (22.01.2021)	Update SLR (12.11.2024)
		glomerulopathy" OR "Complement-component 3 glomerulopathy" OR "Complement component-3 glomerulopathy" OR "Complement-component-3 glomerulopathy" OR "complement 3 glomerulopathy" OR "complement-3 glomerulopathy"):ti,ab,kw (Word variations have been searched)		
	6.	((dense NEAR/2 deposit NEAR/2 disease) OR (c3 NEAR/2 glomerulo*) OR (complement NEAR/2 glomerulo*) OR ("complement-3" NEAR/2 glomerulo*) OR ("complement 3" NEAR/2 glomerulo*) OR ("component 3" NEAR/2 glomerulo*) OR ("component-3" NEAR/2 glomerulo* OR (component NEAR/2 glomerulo*))) :ti,ab,kw (Word variations have been searched)	11	55
	7.	((("membranoproliferative glomerulonephritis" NEAR/2 "type ii") OR ("membranoproliferative glomerulonephritis" NEAR/2 "type 2") OR ("mesangiocapillary glomerulonephritis" NEAR/2 "type ii") OR ("mesangiocapillary glomerulonephritis" NEAR/2 "type 2")) :ti,ab,kw (Word variations have been searched)	1	1
	8.	((("type ii" NEAR/2 mpgn) OR (mpgn NEAR/2 ii) OR (ddd NEAR/2 "mpgn ii") OR ("type 2" NEAR/2 mpgn) OR ("mpgn 2") OR (ddd NEAR/2 "mpgn 2")) :ti,ab,kw (Word variations have been searched)	2	3
	9.	OR #4-#8 (Word variations have been searched)	39	89
Utility and HRQoL outcomes	10.	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	1,270	2,432
	11.	MeSH descriptor: [Quality of Life] explode all trees	24,223	45,212
	12.	MeSH descriptor: [Patient reported outcome Measures] explode all trees	625	1,956
	13.	MeSH descriptor: [Health Status] explode all trees	29,828	53,826
	14.	MeSH descriptor: [Patient Preference] explode all trees	765	1,227
	15.	MeSH descriptor: [Patient Satisfaction] explode all trees	12,153	15,789
	16.	MeSH descriptor: [Surveys and Questionnaires] explode all trees	54,547	78,977
	17.	MeSH descriptor: [Health survey] explode all trees	29,763	41,119
	18.	MeSH descriptor: [Treatment Outcome] explode all trees	139,925	206,471

Term group	#	Search Term	Original SLR (22.01.2021)	Update SLR (12.11.2024)
	19.	MeSH descriptor: [Sickness Impact Profile] explode all trees	539	639
	20.	MeSH descriptor: [Health Status Indicators] explode all trees	22,157	29,895
	21.	MeSH descriptor: [Value of Life] explode all trees	33	49
	22.	[OR #10-#21] (Word variations have been searched)	192,359	293,026
	23.	utility:ti,ab,kw (Word variations have been searched)	46,256	66,394
	24.	("quality of life" OR qol OR hrqol):ti,ab,kw (Word variations have been searched)	115,379	175,104
	25.	#23 AND (#11 OR #24) (Word variations have been searched)	7,263	11,254
	26.	((("quality adjusted life" NEXT year*) OR ("quality-adjusted-life" NEXT year*) OR ("quality adjusted-life" NEXT year*) OR ("quality-adjusted life" NEXT year*) OR ("adjusted life" NEXT year*) OR qaly OR qaly* OR qal* OR (adjusted NEAR/2 life year*)):ti,ab,kw (Word variations have been searched)	5,739	8,458
	27.	((("quality adjusted life" NEXT expectancy*) OR ("quality-adjusted-life" NEXT expectancy*) OR ("quality adjusted-life" NEXT expectancy*) OR ("quality-adjusted life" NEXT expectancy*) OR ("quality adjusted life" NEXT expectancy*) OR qale* OR quale* OR "quality adjusted survival" OR "quality-adjusted-survival" OR "quality- adjusted survival" OR "quality adjusted- survival" OR (life NEXT year*)):ti,ab,kw (Word variations have been searched)	5,811	8,463
	28.	((quality NEXT time*) OR qtime* OR ("quality adjusted life" NEXT day*) OR ("quality-adjusted-life" NEXT day*) OR ("quality adjusted-life" NEXT day*) OR ("quality adjusted life" NEXT day*) OR ("quality-adjusted life" NEXT day*) OR qald*):ti,ab,kw (Word variations have been searched)	97	811
	29.	((health* NEAR/2 year* NEAR/2 equivalent*) OR hye* OR hql* OR hqol* OR h qol* OR hrqol* OR (hr NEXT qol*) OR "health related quality of life" OR "health-related-quality-of-life" OR "health- related-quality-of life" OR "health-related- quality of-life" OR "health-related quality-of life" OR "health-related quality-of-life" OR "health related-quality of life" OR "health related-quality-of-life" OR "health related- quality of life" OR "health-related quality of life" OR "health-related QoL" OR hrql OR	115,533	175,369

Term group	#	Search Term	Original SLR (22.01.2021)	Update SLR (12.11.2024)
		"quality of life" OR qol* OR "quality-of-life" OR "quality-of life" OR "quality of-life" OR "quality of life index"):ti,ab,kw (Word variations have been searched)		
	30	((("patient-reported" NEXT outcome*) OR ("patient reported" NEXT outcome*) OR PRO OR ("self reported" NEXT outcome*) OR ("self-reported" NEXT outcome*) OR morbid* OR mortalit* OR "caregiver burden" OR "caregiver burnout"):ti,ab,kw (Word variations have been searched)	137,803	190,736
	31	("health status" OR "patient preference" OR (visual NEXT analog* NEXT scale*) OR "patient satisfaction" OR Instrument* OR questionnaire* OR "sickness impact profile" OR rosier OR vignette* OR pqol OR "Perceived Quality of Life Scale" OR ("nottingham health" NEXT profile*) OR "functional status questionnaire" OR "duke health profile" OR ("dartmouth coop functional health" NEXT assessment*) OR "assessment quality of life" OR aqol* OR "daily life activity" OR "ADL disability" OR "Activities of daily living disability" OR Psychology OR Psychometric* OR "Health survey" OR "Treatment outcome"):ti,ab,kw (Word variations have been searched)	429,477	611,711
	32	(utility NEAR/3 (score* OR valu* OR health* OR cost* OR measur* OR disease* OR mean* OR gain* OR index* OR estimate* OR outcome* OR weight* OR analysis OR data OR elicit* OR evaluat* OR unit* OR loss* OR lost OR indices OR calculate* OR range* OR increment* OR decrement* OR decreas* OR increas* OR expenditure* OR information OR instrument* OR life OR overall OR report* OR scale* OR scoring OR state* OR status OR caregiver)):ti,ab,kw (Word variations have been searched)	16,044	22,940
	33	((instrument* NEAR/3 "quality of life") OR (preference* NEAR/3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument*)):ti,ab,kw (Word variations have been searched)	2,330	3,289
	34	(hui* or hui1 or hui2 or hui3 or (health NEAR/2 (utilit* or index)) or utilit* or (health NEXT utilit* NEXT index) or (utilit* NEXT index) or (health NEXT utilit*) or (multiattribute* NEXT utility) or (multi NEXT attribute* NEXT utility) or "multi-attribute-utility" or "multi attribute-utility" or mau or disutilit* or (dis NEXT utilit*) or (index NEAR/2 (wellbeing or "well-being" OR "well being")) or (quality NEAR/2 (wellbeing or	20,823	28,657

Term group	#	Search Term	Original SLR (22.01.2021)	Update SLR (12.11.2024)
		"well-being" OR "well being")) or qwb*):ti,ab,kw (Word variations have been searched)		
	35.	("time-trade-off" OR "time trade-off" OR "time-trade off" OR "time trade off" OR "time tradeoff" OR tto OR (standard NEXT gamble*) OR "rating scale" OR "magnitude index" OR "willingness to pay" OR "willingness-to-pay" OR "willingness-to pay" OR "willingness to-pay" OR wtp OR "discrete choice experiment" OR "discrete-choice-experiment" OR "discrete choice-experiment" OR dce OR "conjoint analysis" OR "best worst scaling" OR "best-worst-scaling" OR "best-worst scaling" OR "best worst-scaling"):ti,ab,kw (Word variations have been searched)	48,089	66,434
	36.	((disability or quality) NEAR/2 adjusted) OR (disability NEAR/2 life) OR "disability adjusted life year" OR daly*):ti,ab,kw (Word variations have been searched)	6,203	9,102
	37.	((illness NEXT state*) OR (health NEAR/2 stat*) OR (health NEXT state* NEXT utilit*) OR HSU OR (health NEXT state* NEXT value*) OR HSV OR ("health state utility" NEXT value*) OR HSUV* OR (health NEXT state* NEXT preference*) OR (utility NEXT assessment*) OR (utility NEXT measure*) OR ("preference based") OR (health NEAR/2 preference) OR ("utility based") OR ("cost utility" NEXT stud*) OR (utilit* NEXT stud*) OR (disbenefit)):ti,ab,kw (Word variations have been searched)	21,373	30,208
	38.	("eq-5d" OR eq5d OR "eq-5" OR "eq5-d" OR eq NEXT 5d* OR eq5d* OR "eq5 d" OR "euro qual" OR euroqual OR "euro qol" OR euroqol* OR "euro qol5d" OR euroqol5d OR "euro qual" OR euroqual OR "euro qual5d" OR euroqual5d OR "EuroQOL 5-Dimension" OR "european quality of life" OR eurqol OR eur?qul OR (euro* NEXT "quality of life") OR "european qol"):ti,ab,kw (Word variations have been searched)	9,850	16,523
	39.	("sf-36" OR sf36 OR "sf 36" OR "short form 36" OR "short form-36" OR "short-form 36" OR "short form-thirty-six" OR "short form thirty six" OR "short form thirty-six" OR "short form-thirty six" OR "36-Item Short Form Survey" OR "shortform 36" OR "short form36" OR shortform36 OR "shortform thirty six"):ti,ab,kw (Word variations have been searched)	13,683	19,324

Term group	#	Search Term	Original SLR (22.01.2021)	Update SLR (12.11.2024)
	40.	("sf-6d" OR "sf6d" OR "sf 6d" OR "short form 6d" OR "short form-6d" OR "short form-six d" OR "short form six d" OR sf6 OR "short form 6" OR "shortform 6" OR "shortform six" OR "short form six" OR "sf-8" OR "sf8" OR "sf 8" OR "sf eight" OR "sf-eight" OR "short form 8" OR "short form-8" OR "short form-eight" OR "short form eight" OR "shortform 8" OR "sf-12" OR "sf12" OR "sf 12" OR "shortform 12" OR "short form-12" OR "shortform twelve" OR "12-Item Short Form Survey" OR "short form 12" OR "sf16" OR "sf 16" OR "short form 16" OR "short form-16" OR "shortform 16" OR "sf-20" OR "sf20" OR "sf 20" OR "sf twenty" OR "sf-twenty" OR "short form 20" OR "short form-20" OR "shortform 20" OR 15d OR "15-d" OR "15 d" OR "15 dimension"):ti,ab,kw (Word variations have been searched)	5,200	6,343
	41.	("eq-3d" OR "eq-3" OR eq NEXT 3d* OR "euro qol" OR euroqol OR "euro quol3d" OR "eqvas" OR "eq vas"):ti,ab,kw (Word variations have been searched)	4,120	6,343
	42.	("Kidney Disease Quality of Life Questionnaire" OR KDQoL or "KD QOL" or "KD-QOL" or "kidney-disease-quality-of-life" or "kidney disease-quality-of-life" or "kidney disease quality-of-life" or "kidney-disease-quality-of life" or "kidney-disease quality of life" or "kidney disease-quality of life"):ti,ab,kw (Word variations have been searched)	239	418
	43.	("eq-5d-5l" OR eq5d5l OR "eq 5d 5l" OR "eq5d 5l" OR "eq-5d 5l" OR "eq5d-5l" OR "eq 5d- 5l" OR "euroqol 5 dimension-5 level" OR euro?qol5d-5l OR "eq 5d5l" OR "eq 5d3l" OR "eq-5d-3l" OR eq5d3l OR "eq 5d 3l" OR "eq5d 3l" OR "eq-5d 3l" OR "eq5d-3l" OR "eq 5d-3l" OR "euroqol-5dimension-3 level" OR "euroqol 5 dimension-3 level" OR "euroqol-5dimension 3 level"):ti,ab,kw (Word variations have been searched)	2,635	5,945
	44.	("Functional Assessment of Chronic Illness Therapy-Fatigue" OR "FACIT-fatigue" OR ("FACIT-fatigue" NEXT score*) OR ("FACIT fatigue" NEXT score*) OR "FACIT-fatigue-scale" OR "FACIT-fatigue scale" OR "FACIT fatigue-scale" OR "FACIT-F"):ti,ab,kw (Word variations have been searched)	877	1,601
	45.	(PGIS OR "Patient Global Impression of Severity" OR ("patient global" NEAR/2	208	453

Term group	#	Search Term	Original SLR (22.01.2021)	Update SLR (12.11.2024)
		"severity")):ti,ab,kw (Word variations have been searched)		
	46.	#22 OR #25 OR (OR #26-#45) (Word variations have been searched)	610,401	86,0374
Initial hits	47.	#9 AND #46 (Word variations have been searched)	12*	20
Update**	48	#47 with Cochrane Library publication date from Jan 2021 to present, (Word variations have been searched)	NA	8**

Abbreviations: CDSR: Cochrane database of systematic reviews; CENTRAL: Cochrane Central Register of Controlled Trials; HRQoL: health-related quality of life; SLR: systematic literature review.

Footnotes: *Original SLR: from inception to 22nd January 2021. **Update: January 2021 to 12th November 2024.

Table 3. Corrected version of Appendix G; Table 4: Search strategy for the Cochrane Library databases for the original and update cost and HCRU SLRs (via Cochranelibrary.com)

Term group	#	Search Term	Original SLR (11.02.2021)	SLR update (10.10.2024)
Disease	1.	MeSH descriptor: [Glomerulonephritis] explode all trees	910	1,323
	2.	MeSH descriptor: [Glomerulonephritis, Membranoproliferative] explode all trees	20	28
	3.	MeSH descriptor: [Complement C3] explode all trees	286	339
	4.	(#1 OR #2) AND #3 (Word variations have been searched)	16	18
	5.	("c3 glomerulopathy" or C3G or "dense deposit disease" or "dense-deposit-disease" or "dense deposit-disease" or "dense-deposit disease" or "c3 glomerulonephritis" or C3GN or "Complement component 3 glomerulopathy" or "Complement-component 3 glomerulopathy" or "Complement component-3 glomerulopathy" or "Complement-component-3 glomerulopathy" or "complement 3 glomerulopathy" or "complement-3 glomerulopathy"):ti,ab,kw (Word variations have been searched)	22	70
	6.	((dense NEAR/2 deposit NEAR/2 disease) OR (c3 NEAR/2 glomerulo*) OR (complement NEAR/2 glomerulo*) OR (complement-3 NEAR/2 glomerulo*) OR ("complement 3" NEAR/2 glomerulo*) OR ("component 3" NEAR/2 glomerulo*) OR ("component-3" NEAR/2 glomerulo*) OR (component NEAR/2 glomerulo*)):ti,ab,kw (Word variations have been searched)	11	54
	7.	((("membranoproliferative glomerulonephritis" NEAR/2 "type ii" OR "membranoproliferative glomerulonephritis" NEAR/2 "type 2" OR "mesangiocapillary glomerulonephritis" NEAR/2 "type ii" OR "mesangiocapillary	1	1

Term group	#	Search Term	Original SLR (11.02.2021)	SLR update (10.10.2024)
		glomerulonephritis" NEAR/2 "type 2")):ti,ab,kw (Word variations have been searched)		
	8.	((("type ii" NEAR/2 mpgn OR "mpgn" NEAR/2 ii OR ddd NEAR/2 "mpgn ii" OR "type 2" NEAR/2 mpgn OR "mpgn 2" OR ddd NEAR/2 "mpgn 2"))):ti,ab,kw (Word variations have been searched)	2	3
	9.	{OR #4-#8} (Word variations have been searched)	39	88
Cost outcomes	10.	MeSH descriptor: [costs and cost analysis] explode all trees	10,591	16,718
	11.	MeSH descriptor: [Cost of Illness] explode all trees	819	1,192
	12.	MeSH descriptor: [Cost Allocation] explode all trees	3	8
	13.	MeSH descriptor: [Cost Control] explode all trees	587	818
	14.	MeSH descriptor: [Cost Savings] explode all trees	433	618
	15.	MeSH descriptor: [Deductibles and Coinsurance] explode all trees	21	33
	16.	MeSH descriptor: [Direct Service Costs] explode all trees	74	90
	17.	MeSH descriptor: [Health Care Costs] explode all trees	3,449	4,882
	18.	MeSH descriptor: [Drug Costs] explode all trees	768	1,171
	19.	MeSH descriptor: [Hospital Costs] explode all trees	621	811
	20.	MeSH descriptor: [Hospital Charges] explode all trees	85	101
	21.	MeSH descriptor: [Economics] explode all trees	12,579	20,283
	22.	MeSH descriptor: [Employer Health Costs] explode all trees	8	10
	23.	MeSH descriptor: [Cost Sharing] explode all trees	37	66
	24.	MeSH descriptor: [Capital Expenditures] explode all trees	3	3
	25.	MeSH descriptor: [Value of Life] explode all trees	33	49
	26.	MeSH descriptor: [Economics, Hospital] explode all trees	719	932
	27.	MeSH descriptor: [Economics, Medical] explode all trees	62	77
	28.	MeSH descriptor: [Economics, Nursing] explode all trees	12	14
	29.	MeSH descriptor: [Financing, Organized] explode all trees	1,832	3,150

Term group	#	Search Term	Original SLR (11.02.2021)	SLR update (10.10.2024)
	30.	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65	139
	31.	MeSH descriptor: [Health Expenditures] explode all trees	220	386
	32.	MeSH descriptor: [Fees and Charges] explode all trees	251	346
	33.	MeSH descriptor: [Fees, Medical] explode all trees	36	42
	34.	MeSH descriptor: [Nursing, Supervisory] explode all trees	35	37
	35.	MeSH descriptor: [Financial Support] explode all trees	126	342
	36.	MeSH descriptor: [Financial Management] explode all trees	247	421
	37.	MeSH descriptor: [Healthcare Financing] explode all trees	6	16
	38.	MeSH descriptor: [Budgets] explode all trees	27	67
	39.	(cost* or costing or "cost analysis" OR "cost variable" OR expense* OR expendi* OR fiscal OR fund* OR "cost per patient treated" OR "financial management" OR "health care financing" OR "economic evaluation" OR "economic aspect" OR "socioeconomics" OR "economic burden" OR (Nursing NEXT Economic*) OR (Medical NEXT Economic*) OR (Pharmaceutical NEXT Economic*) OR (Hospital NEXT Economic*) OR ("Medical savings" NEXT account*) OR (Health NEXT expenditure*) OR (Capital NEXT expenditure*) OR "Value of life" OR (Organized NEXT Financ*) OR (medical NEXT fee*) OR (nursing NEXT supervisor*) OR "Financial Support"):ti,ab,kw (Word variations have been searched)	114,503	157,909
	40.	(economic* OR pharmaco?economic* OR (drug NEXT cost*) OR price* OR pricing* OR saving* OR time OR financ* OR fee* OR afford* OR money OR monetary OR (health NEXT economic*) OR budget* OR (deductibles NEAR/2 coinsurance)):ti,ab,kw (Word variations have been searched)	530,278	719,572
	41.	(valu* NEAR/2 (money OR economic OR monetary OR life)):ti,ab,kw (Word variations have been searched)	862	1,253
	42.	((caregiver* OR care* OR famil*) NEAR/3 (cost OR expendi* OR expense* OR time)):ti,ab,kw (Word variations have been searched)	14,245	18,792
	43.	((charge* OR cost*) NEAR/3 (hospital* OR nurse OR prescription OR "health care" OR "health-care" OR healthcare OR drug OR treat* OR therap* OR illness OR estimate OR unit OR allocation OR analysis OR burden* OR outcome* OR saving* OR shar* OR control* OR	52,435	68,927

Term group	#	Search Term	Original SLR (11.02.2021)	SLR update (10.10.2024)
		variable OR effective* OR utilit* OR benefit* OR minimi* OR direct* OR "direct medical" OR "direct service" OR "medical direct" OR (direct NEXT non?medical) OR indirect OR societ* OR total OR "employer health"))):ti,ab,kw (Word variations have been searched)		
	44.	((high* OR low*) NEAR/2 (cost* OR pric* OR charge* OR budget OR fee*))):ti,ab,kw (Word variations have been searched)	12,951	17,579
	45.	((inpatient* OR in-patient* OR outpatient* OR out-patient* OR (hospital NEXT patient*) OR hospital-patient* OR "emergency-room" OR "emergency room" OR "emergency department" OR "emergency-department" OR er OR ed OR hospital*) NEAR/2 (cost* OR pric* OR charge* OR budget OR fee* OR expen*))):ti,ab,kw (Word variations have been searched)	6,423	8,489
	46.	((cost* OR charge*) NEAR/5 (transplant* OR transplantation* OR graft* OR *transplant)):ti,ab,kw (Word variations have been searched)	487	598
	47.	((cost* OR charge*) NEAR/5 (dialysis OR dialys* OR hemodialysis OR haemodialysis OR "peritoneal dialysis")):ti,ab,kw (Word variations have been searched)	243	304
	48.	((cost* OR charge*) NEAR/5 (ESKD OR ESRD)):ti,ab,kw (Word variations have been searched)	38	43
	49.	((cost* OR charge*) NEAR/5 (end-stage kidney disease)):ti,ab,kw (Word variations have been searched)	3,644	4,825
	50.	((cost* OR charge*) NEAR/5 (end-stage renal disease OR ("Chronic kidney" NEXT disease*) OR CKD OR "Estimated Glomerular Filtration Rate" OR eGFR)):ti,ab,kw (Word variations have been searched)	3,689	4,889
	51.	OR #10-#50) (Word variations have been searched)	585,410	790,897
HCRU outcomes	52.	MeSH descriptor: [Resource Allocation] explode all trees	73	131
	53.	MeSH descriptor: [Patient Acceptance of Health Care] explode all trees	17,451	23,491
	54.	MeSH descriptor: [Health Resources] explode all trees	440	597
	55.	MeSH descriptor: [Hospitalization] explode all trees	14,097	20,711
	56.	MeSH descriptor: [Inpatients] explode all trees	956	1,681
	57.	MeSH descriptor: [Outpatients] explode all trees	1,199	2,022
	58.	MeSH descriptor: [Intensive Care Units] explode all trees	3,633	6,208

Term group	#	Search Term	Original SLR (11.02.2021)	SLR update (10.10.2024)
	59.	MeSH descriptor: [Emergency Service, Hospital] explode all trees	2,406	4,022
	60.	(resource* OR healthcare OR "health care" OR service* OR (health NEXT service*) OR (health NEXT resource*) OR drug OR Medic*) NEAR/5 (use* OR usage OR utili* OR consum*):ti,ab,kw (Word variations have been searched)	85,357	115,956
	61.	((("healthcare resource" NEXT utili*) OR ("health resource" NEXT utili*) OR hru):ti,ab,kw (Word variations have been searched)	624	943
	62.	((resource NEXT utili*) OR (healthcare NEXT utili*) OR "resource allocation" OR resource* OR utili* OR hospitali* OR "length of stay" OR los OR ("length of" NEXT hospitali*) OR "hospital-admission" OR consult* OR visit* OR (health NEXT resource*) OR "Patient Acceptance of Health Care"):ti,ab,kw (Word variations have been searched)	225,324	310,034
	63.	((("primary care" OR primarycare OR physician OR clinic* OR unschedule* OR Office) NEAR/2 visit*) OR "prolonged stay" OR (acute NEXT hospitali*) OR ("non-acute" NEXT hospitali*) OR "intensive care unit" OR icu):ti,ab,kw (Word variations have been searched)	34,922	49,937
	64.	("emergency department" OR "emergency room" OR "emergency ward" OR "emergency unit" OR ed OR er OR ("emergency room" OR "emergency department" OR "emergency ward" OR "emergency unit" OR ed OR er) NEAR/2 visit*):ti,ab,kw (Word variations have been searched)	27,802	36,711
	65.	(outpatient OR "hospital outpatient" OR "GP contacts" OR (drug* NEXT prescri*) OR (("hospital outpatient" OR outpatient or GP OR "general practitioner" OR physician OR specialist) NEAR/2 visit*):ti,ab,kw (Word variations have been searched)	43,653	56,439
	66.	(inpatient* OR (in NEXT patient*) OR "in patient hospitali" OR (hospitali* NEXT rate) OR rehospitali* OR admission* OR admit*):ti,ab,kw (Word variations have been searched)	395,621	517,564
	67.	{OR #52-#66} (Word variations have been searched)	635,467	837,678
Cost and HCRU outcomes	68.	#51 OR #67 (Word variations have been searched)	941,974	1,261,072
Primary	69.	#9 AND #68 (Word variations have been searched)	29	58
Update	70.	#69 with Cochrane Library publication date from Jan 2021 to present, (Word variations have been searched)	NA	35

Abbreviations: HCRU: healthcare resource utilisation; NA: not available; SLR: systematic literature review.

A 2. Please confirm that Embase was searched via the Embase.com interface, rather than on Ovid, as stated in Appendix E; Tables 1 and 3 and Appendix F; Tables 1 and 2.

The references to Ovid in Appendix E (Tables 1 and 3) and Appendix F (Tables 1 and 2) were included in error. We apologise for this inaccuracy and can confirm that Embase was searched via the Embase.com interface.

Decision problem

A 3. Priority question. In Table 1 of the company submission (CS), the company stated that eculizumab is considered of limited relevance as a comparator because in UK clinical practice its use is uncommon, with the NHS England commissioning policy restricting use to a small subgroup among patients with post-transplant recurrence, and its use is limited to patients with highly aggressive recurrent disease. Please include eculizumab as a comparator in clinical effectiveness analyses and a cost effectiveness analysis for the appropriate subgroup as used in UK clinical practice, or exclude this subgroup from the decision problem.

There is no head-to-head data for iptacopan versus eculizumab in C3G, and, as further explained in the response to clarification question A11, an indirect treatment comparison is deemed infeasible. It was therefore not possible to include eculizumab as a comparator within the cost-effectiveness model.

The use of eculizumab for C3G in UK clinical practice is restricted by an NHS England commissioning policy to a subset of patients with highly aggressive post-transplant recurrence of C3G.¹ Amongst others, the NHS England criteria require evidence of a significant decline of transplant function (>20% decline in eGFR) within the previous three months before eculizumab can be initiated.¹ Treatment with iptacopan, on the other hand, can be started as soon as recurrence is diagnosed via biopsy of the transplanted kidney, before the onset of clinical signs such as eGFR decline; this is in line with the available clinical trial evidence from the iptacopan Phase 2 study (see CS Section 2.5.1) and the draft SmPC (section 4.2).^{2, 3} Given that transplanted patients are monitored closely, C3G recurrence is usually diagnosed early, and UK clinicians advised that they would want to start iptacopan as soon as possible after histological diagnosis of recurrence.^{4, 5} This places iptacopan potentially at a much earlier point in the treatment pathway than eculizumab, which requires evidence of significant eGFR decline post-transplant before it can be initiated.^{4, 5} This further reduces the relevance of eculizumab as a comparator for iptacopan.

In potential rare cases where disease recurrence is diagnosed late, clinical signs including significant eGFR decline are already present and the NHS England eculizumab criteria would be met, iptacopan would likely still be preferred over eculizumab given its (anticipated) licence in C3G, targeted mode of action, and availability of clinical trial data demonstrating efficacy in C3G.^{4, 5} Therefore, this subgroup should not be excluded from the decision problem. However, as highlighted in the CS, over the past seven years on average only 1 C3G patient per year has received eculizumab, and the role of eculizumab in C3G is expected to decrease further if iptacopan can be used earlier in the disease course.^{4, 6} Consequently, Novartis considers the inability to provide a cost-effectiveness analysis versus eculizumab as a minor limitation of this submission, given that clinical scenarios where iptacopan and eculizumab would be considered

at the same point in the treatment pathway will be extremely rare (far lower than 1 patient per year).

Systematic review

A 4. Data extraction was conducted by one reviewer and then checked by a second. Please confirm how disagreements were resolved?

Any discrepancies in data extraction were discussed between the two reviewers. If consensus could not be reached, a third independent reviewer was consulted to make a final decision.

A 5. Quality assessments were conducted by one reviewer and then checked by a second. Please confirm how disagreements were resolved.

Any discrepancies in quality assessment were discussed between the two reviewers. If consensus could not be reached, a third independent reviewer was consulted to make a final decision.

Clinical effectiveness evidence

A 6. Priority question: Based on Figure 12 of CS (eGFR CfB up to Month 12 by treatment group; page 56 of CS) and Figure 13 of CS (eGFR CfB up to Month 12, adjusted for baseline UPCR; page 57 of CS), there was a big increase in change from baseline of eGFR at day-14 for the iptacopan arm of the APPEAR-C3G trial. Please provide an explanation for this big increase in change from baseline of eGFR at day-14 for the iptacopan arm of the APPEAR-C3G trial.

C3G patients experience overactivation of the complement alternative pathway which leads to deposition of complement component 3 (C3) within the glomeruli, triggering inflammation.⁷ Two UK clinicians consulted on a call to obtain clinical expert input for Novartis' response to the EAG's clarification questions assumed that the numerical increase in eGFR at Day 14 following iptacopan initiation is due to the rapid resolution of the intense inflammation in the kidney of C3G patients through alternative pathway inhibition.⁸ Biomarker results from APPEAR-C3G demonstrated the rapid inhibition of the alternative pathway by iptacopan, with serum C3 levels increasing from baseline to Day 14 by 249% and urine soluble C5b-9 decreasing from baseline to Day 30 by 92.1%.⁹

The increase in eGFR on Day 14 of iptacopan treatment was transient and short-term, with the Day 30 mean eGFR value on a similar level as subsequent measurements, as visible from Figures 12 and 13 in the CS. A sensitivity analysis on eGFR slope which excluded Day 14 measurements from the analysis confirmed that the short-term, temporary increase in mean eGFR at the start of iptacopan treatment did not impact longer-term eGFR slope estimates (Table 4).

Table 4: APPEAR-C3G eGFR slope sensitivity analysis excluding Day 14 measurements

Analysis	Annual eGFR slope, mL/min/1.73m ² /year (95% CI)		
	SoC	Iptacopan	Iptacopan treatment effect
Base case analysis (N=74) - SoC: pre-iptacopan data, up to 2.5 years - Iptacopan: on-iptacopan data, up to 2 years treatment duration	-7.224 (-10.101, -4.348)	-0.289 (-3.884, 3.305)	6.935 (3.481, 10.390)
Sensitivity analysis excluding Day 14 measurements (N=74) - SoC: pre-iptacopan data, up to 2.5 years - Iptacopan: on-iptacopan data, up to 2 years treatment duration			

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; SoC, standard of care.

Sources: Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 1 Table 2-1.2);¹⁰ Novartis Data on File. 2024 (Clarification questions supplementary analyses – Section A6).¹¹

A 7. Priority question: In Figure 14 of CS (eGFR slope change with iptacopan treatment; page 59 of CS), eGFR slope change with iptacopan treatment (post-LNP023 treatment) of the APPEAR-C3G trial was based on the overall data of double-blind period and open-label period of APPEAR-C3G trial. Please provide a separate analysis for the double-blind period of the APPEAR-C3G trial as well as a separate analysis for the open-label period of the APPEAR-C3G trial.

An eGFR slope change analysis for the 6-month double-blind period of the APPEAR-C3G trial, split by treatment arms, is presented in Figure 15 and Table 16 of the CS. These results are replicated below in Table 5, alongside eGFR slope estimates (generated in a separate model) for the 6-month open-label treatment period, where all patients received open-label iptacopan.

As visible in Table 5, patients allocated to the iptacopan arm had a steeper mean eGFR decline pre-randomisation than patients allocated to the placebo arm, consistent with baseline characteristics suggesting a more severe disease phenotype in the iptacopan arm than in the placebo arm (CS Table 7),^{4, 9} which may impact comparability between arms.⁴

Annual eGFR slope estimates for patients treated with iptacopan in the double-blind period (-0.025 mL/min/1.73m²) and patients treated with iptacopan in the open-label period (mL/min/1.73m²) were similar. However, given that UK clinicians advised that a time frame of 6 months may be too short to robustly estimate changes in eGFR,⁴ these estimates by treatment period (each based on 6 months of data) should be interpreted with caution, with eGFR slope analyses based on longer follow-up considered more robust and meaningful by clinical advisors.^{4, 8}

Table 5: Model estimated eGFR (mL/min/1.73m²) slopes per year by study arm and treatment period (FAS)

	Pre-randomisation period	Double-blind treatment period		Open-label treatment period*	
Study arm	eGFR slope per year (95% CI)	Study treatment	eGFR slope per year (95% CI)	Study treatment	eGFR slope per year (95% CI)
Iptacopan (N=38)	-10.753 (-15.510, -5.996)	Iptacopan	-0.025 (-6.929, 6.878)	Iptacopan	
Placebo (N=36)	-7.641 (-12.279, -3.003)	Placebo	-3.079 (-10.131, 3.973)	Iptacopan	
All patients (N=74)	-	-	-	Iptacopan	

*eGFR slopes for open-label period were estimated in a separate model.

eGFR slopes per year were analysed using a linear mixed effects model including treatment as a factor, time (analysis day before or day after study Day 1) as a continuous covariate, treatment*time as a fixed effect, participant-level intercept and slope (time) as random effects. Intercurrent events were handled with a treatment policy strategy.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; N, number of all patients included in the analysis.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data Table 14.2–16.2.1);⁹ Novartis Data on File. 2025 (Clarification questions supplementary analyses – Section A7).¹¹

A 8. Priority question: Based on Table 7 of CS (APPEAR-C3G baseline demographics and disease characteristics; page 42-44 of CS), there were imbalances in relevant baseline characteristics between the intervention arm and control arm of the APPEAR-C3G trial. Please discuss the impact of these imbalances in relevant baseline characteristics between the two arms on the results being derived from the APPEAR-C3G trial.

As noted in the CS, there were imbalances between the APPEAR-C3G treatment arms for some baseline disease characteristics; patients randomised to the iptacopan arm had notably higher UPCR and lower eGFR at baseline, compared with those from the placebo arm. Furthermore, there were a greater number of participants with baseline nephrotic range proteinuria (≥ 3 g/g) in the iptacopan arm than in the placebo arm.^{4, 9} The baseline imbalances suggest a more severe disease phenotype in the participants in the iptacopan arm. This was also noted by UK clinicians participating in an advisory board, and they suggested that due to this, comparisons between iptacopan and placebo groups may therefore underestimate the iptacopan treatment effect.⁴

Due to these imbalances, several post-hoc sensitivity analyses were conducted. Pages 50–51 of the CS (Table 11) present post-hoc sensitivity analyses for the primary endpoint, change from baseline (CfB) in UPCR; these results are replicated below in Table 6.⁹ The results of these post-hoc sensitivity analyses were consistent with the results of the primary analysis, suggesting that these baseline imbalances did not impact the UPCR endpoint.⁹

Table 6: Post-hoc sensitivity analyses for primary endpoint change from baseline in UPCR at Month 6 (FAS)

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		% Reduction (95% CI)	1-sided p-value
Log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at Month 6	Primary analysis		
	Primary analysis	35.1 (13.8, 51.1)	0.0014
	Post-hoc sensitivity analyses		
	Post-hoc sensitivity analysis 1: Adjustment for baseline eGFR (mL/min/1.73 m ²)	35.0 (13.4, 51.2)	0.0016
	Post-hoc sensitivity analysis 2: Adjustment for age group at C3G diagnosis ^a	35.8 (14.2, 52.0)	0.0014
	Post-hoc sensitivity analysis 3: Adjustment for C3G subtype at diagnosis ^b	38.4 (17.5, 54.1)	0.0006

^aAge group at C3G diagnosis was categorised as <18 years and ≥18 years. ^bC3G subtype at diagnosis was categorised as C3GN and other.

Abbreviations: b.i.d., twice daily; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; UPCR, urine protein-to-creatinine ratio. **Source:** Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-3; Figure 11-4).⁹

The pre-specified analysis of CfB in eGFR included the background immunosuppression stratification factor (corticosteroids and/or mycophenolic acid treatment at randomisation) and baseline eGFR as covariates. Additional post-hoc sensitivity analyses were carried out to assess the impact of adjusting for other baseline covariates where imbalances had been observed, with results shown in Table 7. The adjustments for age at C3G diagnosis or subtype of C3G yielded results consistent with the pre-specified analysis.⁹

However, the CfB in eGFR analysis adjusted for baseline UPCR resulted in a larger numerical improvement for iptacopan versus placebo when compared to the pre-specified analysis, with an adjusted mean difference of 3.20 mL/min/1.73m² for iptacopan versus placebo (95% CI: -1.61, 8.01) compared to the pre-specified analysis with a mean difference of 2.16 mL/min/1.73m² (95% CI: -2.75, 7.06) (see Table 7).⁹

Table 7: Post-hoc sensitivity analyses for secondary endpoint change from baseline in eGFR (mL/min/1.73m²) at Month 6 (FAS)

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		Adj. mean difference (95% CI)	1-sided p-value
Change from baseline in eGFR (mL/min/1.73m ²) at Month 6	Pre-specified analysis		
	Pre-specified analysis	2.156 (-2.749, 7.061)	0.1945
	Post-hoc sensitivity analyses		
	Post-hoc sensitivity analysis 1: Adjustment for baseline UPCR 24h (g/g)	3.199 (-1.614, 8.012)	0.0963

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		Adj. mean difference (95% CI)	1-sided p-value
	Post-hoc sensitivity analysis 2: Adjustment for age group at C3G diagnosis ^a	2.374 (-2.622, 7.369)	0.1759
	Post-hoc sensitivity analysis 3: Adjustment for C3G subtype at diagnosis ^b	2.068 (-2.952, 7.088)	0.2097

^aAge group at C3G diagnosis was categorised as <18 years and ≥18 years. ^bC3G subtype at diagnosis was categorised as C3GN and other.

Abbreviations: b.i.d., twice daily; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; UPCR, urine protein-to-creatinine ratio.

Source: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 11-6; Figure 11-11; Table 14.2-3.5).⁹

A 9. Please provide baseline characteristics for all UK based participants in the included evidence.

Patient demographics and disease characteristics at baseline for UK participants in APPEAR-C3G are shown in Table 8.

Table 8: APPEAR-C3G baseline characteristics for UK participants

	Iptacopan (N=1)	Placebo (N=1)	Total (N=9)
Baseline demographics			
Age (years) Mean (SD)	██████████	██████████	██████████
Gender, n (%) Male Female	██████ ██████	██████ ██████	██████ ██████
Race, n (%) White	██████	██████	██████
Region, n (%) Europe	██████	██████	██████
Baseline disease characteristics			
Baseline UPCR 24h (g/mol) Arithmetic mean (SD) Geometric mean (95% CI)	██████████ ██████████ ██████████	██████████ ██████████ ██████████	██████████ ██████████ ██████████
Baseline UPCR 24h [g/g] Arithmetic mean (SD) Geometric mean (95% CI)	██████████ ██████████ ██████████	██████████ ██████████ ██████████	██████████ ██████████ ██████████
Baseline UPCR (24h), n (%) <339 g/mol [3 g/g] ≥339 g/mol [3 g/g]	██████ ██████	██████ ██████	██████ ██████
Baseline eGFR [mL/min/1.73m²] Mean (SD)	██████████	██████████	██████████

	Iptacopan (N=1)	Placebo (N=1)	Total (N=9)
Baseline eGFR, n (%) <90 mL/min/1.73m ² ≥90 mL/min/1.73m ²			
Baseline eGFR, n (%) <60 mL/min/1.73m ² ≥60 mL/min/1.73m ²			
Baseline C3 [mg/L] Arithmetic mean (SD) Geometric mean (95% CI)			
Baseline C3, n (%) <450 mg/L ≥450 mg/L			
Hypertension^a, n (%) Yes No			
Age at C3G diagnosis, years Mean (SD)			
Age at C3G diagnosis, n (%) <18 years ≥18 years			
Time since first C3G diagnosis, years Mean (SD)			
Time since first C3G diagnosis, n (%) <2 years ≥2 years			
C3G subtype at diagnosis, n (%) C3GN Unknown			

Footnotes: Baseline 24h UPCR refers to UPCR as measured by the geometric mean of two 24h urine collections at baseline/Day 1. Baseline total urinary protein 24h refers to total urinary protein as measured by the geometric mean of two 24h urine collections at baseline/Day 1. Baseline eGFR was defined as the arithmetic mean of two eGFR values at Day -15 visit and Day 1 visit. ^aHypertension is defined based on "hypertension at diagnosis" from C3G medical history and the reported hypertension terms from the medical history.

Abbreviations: C3, complement 3; C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; RAS, renin angiotensin system; SD, standard deviation; UK, United Kingdom; UPCR, urine protein-to-creatinine ratio.

Source: Novartis Data on File. 2024 (Clarification questions supplementary analyses – Section A9).¹¹

A 10. Please describe the generalisability of the trial populations to the relevant clinical populations in England and Wales and provide evidence to support the description of the clinical characteristics of the relevant population in England and Wales.

In a discussion in a UK advisory board, clinical experts were aligned that the inclusion criteria of the APPEAR-C3G and Phase 2 trials were valid, and that the trial populations were reflective of patients with C3G seen in UK clinical practice. For example, the advisors agreed that the concomitant medications (including ACEi/ARBs) in APPEAR-C3G were appropriate and representative of management of C3G patients within UK clinical practice, and that C3G patients generally present with UPCR levels well above 1 g/g (≥ 113 mg/mmol).⁴ The trial generalisability to the C3G population in England and Wales was further supported by the fact that several UK study sites had participated in the trials.⁴

A comparison of patient characteristics in APPEAR-C3G⁹ and the C3G population of RaDaR¹² is shown in Table 9. RaDaR reports characteristics at time of diagnosis, as well as at latest follow-up (for prevalent patients at the time of the analysis). Median age at diagnosis was similar in APPEAR-C3G and the RaDaR cohort. Age at latest follow-up was higher in the prevalent RaDaR cohort than in APPEAR-C3G patients at baseline. The lower percentage of females in APPEAR-C3G (36.5%) compared to RaDaR (47%) was noted by UK clinicians as a common finding in clinical trials, especially in young age groups where pregnancy is a concern.⁴

With regards to clinical characteristics, RaDaR patients were, on average, diagnosed with higher UPCR and a lower eGFR, indicating more advanced disease at time of diagnosis, than patients enrolled in APPEAR-C3G. Baseline mean UPCR of APPEAR-C3G participants was higher (3.40 g/g) compared to the prevalent RaDaR cohort (1.73 g/g). This is expected given that APPEAR-C3G focused on a population at higher risk of disease progression, with baseline UPCR ≥ 1 g/g despite treatment with a maximally tolerated dose of ACEi/ARB.⁹ UK clinicians confirmed that the APPEAR-C3G UPCR inclusion criterion was reflective of a population who they would intend to use iptacopan in.⁴ Higher mean eGFR at baseline in APPEAR-C3G patients (94.12 mL/min/1.73m²) than in the prevalent RaDaR cohort (67 mL/min/1.73m²) may partially be related to the higher eGFR at diagnosis compared to UK clinical practice, but is also influenced by the APPEAR-C3G eGFR inclusion criterion of ≥ 30 mL/min/1.73m² at screening.⁹ UK clinicians advised that they would generally want to start iptacopan treatment as soon as possible after C3G diagnosis, to preserve kidney function at the highest possible level, although people with more advanced disease would also be expected to derive benefit from iptacopan.⁴

Overall, UK clinicians confirmed that the patients included in APPEAR-C3G and the Phase 2 study (patients with post-transplant recurrence) reflected patients who they considered would benefit from iptacopan in UK clinical practice and considered the trial data generalisable.⁴

Table 9: APPEAR-C3G and RaDaR disease characteristics

	APPEAR-C3G (N=74)	RaDaR at diagnosis (N=258)	RaDaR at latest follow-up^c (N=240)
Age at C3G diagnosis (years)			
Mean (SD)	23.6 (10.9)	28.9 (20.24)	NR
Median	20.0	21.8	
Current age (years)^a			
Mean (SD)	27.9 (10.68)	NA	40.6 (19.34)
Median	23.0		36.4

	APPEAR-C3G (N=74)	RaDaR at diagnosis (N=258)	RaDaR at latest follow-up ^c (N=240)
Gender, n (%)			
Male	47 (63.5)	139 (54)	128 (53)
Female	27 (36.5)	119 (46)	112 (47)
Race, n (%)			
White	51 (68.9)	203 (79)	186 (78)
Black or African American	2 (2.7)	NR	NR
Asian	18 (24.3)	NR	NR
American Indian or Alaska Native	1 (1.4)	NR	NR
Multiple	1 (1.4)	NR	NR
Other	NR	25 (10)	24 (10)
Unknown	1 (1.4)	30 (12)	30 (13)
UPCR at diagnosis (g/g)		(N=91)	
Arithmetic mean (SD)	3.98 (3.14)	6.04 (11.87) ^b	NR
Current UPCR (g/g)^a			(N=38)
Arithmetic mean (SD)	3.40 (2.07)	NA	1.73 (2.64) ^b
eGFR at diagnosis (mL/min/1.73m²)		(N=109)	
Mean (SD)	110.60 (33.96)	70 (38.1)	NR
Current eGFR (mL/min/1.73m²)^a			(N=62)
Mean (SD)	94.12 (31.61)	NA	67 (40.3)

^a“Current” in relation to APPEAR-C3G refers to values at baseline. ^bReported in mg/mmol in RaDaR data, converted to g/g by dividing by 113. Original reported values: RaDaR at latest follow-up, mean (SD) 196 (297.9) mg/mmol; RaDaR at diagnosis, mean (SD) 682 (1340.8) mg/mmol. ^cPrevalent population. At latest follow-up reflects measurement within the last year. Patients who are on KRT are excluded from the prevalent population laboratory results.

Abbreviations: C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; NA, not applicable; NR, not reported; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

Sources: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Tables 10-3, 10-4, 10-5 and Section 11.2.1.5);⁹ Novartis Data on File. 2024 (C3G RaDaR Priority Analysis, Interim Enrichment Report (December 2024))¹²

Indirect treatment comparison (ITC)

A 11. Priority question: The company stated that ITC analysis for the comparison of iptacopan vs. eculizumab was not feasible because the outcome (eGFR) used in the economic model was not reported in the eculizumab trials. Therefore, please conduct ITC analyses based on other outcomes (e.g. proteinuria) that were reported in the eculizumab trials for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence, by using the post-transplant recurrent cohort of the Phase 2 trial of iptacopan.

The ITC versus eculizumab was not deemed feasible for a number of reasons, as noted in Section 2.9 of the CS with further details provided in Section B.1.7 of Appendix B. These reasons included the small sample sizes of the identified eculizumab trials (4–6 patients each) as well as

the limited generalisability of the eculizumab trial populations to how eculizumab is used in UK clinical practice.

The clinical trials SLR identified three trials which assessed eculizumab for C3G. Two single-arm, single-centre trials from the US and Turkey included 6 C3G patients treated with eculizumab each,¹³⁻¹⁵ while the third single-arm trial from Italy included overall 10 patients, 4 of which had C3G and were treated with eculizumab.¹⁶

None of the studies reported inclusion criteria that were similar to the NHS England Clinical Commissioning Policy, which restricts use of eculizumab in the UK to a subset of patients with post-transplant recurrence of C3G and meeting very specific criteria indicative of highly aggressive disease; this includes evidence of active glomerulonephritis with cellular crescents on kidney biopsy and a >20% decline in eGFR within the previous three months.¹ Therefore, findings from the three international studies identified in the SLR may not be generalisable to eculizumab use in UK clinical practice.

With regards to outcomes, none of the three studies reported eGFR data (the outcome of interest for economic modelling) for patients with C3G treated with eculizumab. An ITC of proteinuria outcomes was not considered meaningful due to marked differences in the eculizumab trial populations and the patients included in the post-transplant recurrent cohort of the iptacopan Phase 2 trial. The three eculizumab trials enrolled patients with proteinuria >3.5 g/day, ≥3 g/day, and >1 g/day, respectively (see Appendix B, Table 11). In contrast, elevated proteinuria was not an inclusion criterion for the post-transplant cohort in the iptacopan Phase 2 trial; accordingly, the enrolled patients' proteinuria levels were predominantly normal at baseline, with a geo-mean of 0.28 g/day.² Therefore, an ITC of proteinuria reduction outcomes was considered not to provide meaningful results.

An ITC of iptacopan versus eculizumab was overall not considered feasible, however, as outlined in the response to clarification question A3, given the very limited role of eculizumab in UK clinical practice, Novartis considers this a minor limitation of this submission.

Adverse events

A 12. The CS stated that approximately half of the serious adverse events (SAEs) were infection-related. Please provide a detailed breakdown of the types and severity of infections observed (e.g., bacterial, viral or fungal). Please also clarify any of these infections related to encapsulated bacteria (e.g., *Neisseria meningitidis*, *Streptococcus pneumoniae*).

Most infections were non-serious and assessed by the investigator as not related to iptacopan. All infections resolved, with patients either continuing study treatment or resuming it after resolution. Importantly, no cases of meningococcal infection were reported.¹⁷

In the broad safety set, ten patients experienced a total of 17 infection-related SAEs whilst on iptacopan.¹⁷ The types of infections reported across the C3G studies are shown in Table 10.

Six of the below SAEs were related to encapsulated bacteria, occurring in a total of four patients. In all cases these were caused by streptococcal infections, with one patient experiencing *Streptococcus gallolyticus* infection (intervertebral discitis), and all others experiencing *Streptococcus pneumoniae* infections. The severity of these SAEs was moderate for two patients and severe for two patients.

Table 10. Infection SAEs reported across C3G studies (broad safety set)

Type of infection Number of SAEs	Severity			Total
	Mild	Moderate	Severe	
Bacterial (encapsulated)	0	4	2	6
Intervertebral discitis		1		1
Pneumonia pneumococcal		1	1	2
Pneumococcal sepsis		1		1
Septic shock			1	1
Streptococcal bacteraemia (evolved to septic shock)		1		1
Bacterial (other)	2	3	0	5
Appendicitis	1			1
Pelvic inflammatory disease		1		1
Pneumonia	1			1
<i>Pneumocystis jiroveci</i> pneumonia		1		1
Pyelonephritis		1		1
Bacterial/viral			1	1
Blood culture positive			1	1
Viral		1		1
Norovirus infection		1		1
Viral (probable)			1	1
Pericarditis			1	1
NR	1	2		3
Enteritis		1		1
Gastroenteritis	1			1
Infected bite		1		1
Total	3	10	4	17

Abbreviations: NR, not reported.

Source: Novartis Data on File (Summary of Clinical Safety, Table 10-2).¹⁷

A 13. The CS stated that three patients discontinued iptacopan due to AEs (all in the open-label extension study), with SAEs determined not to be related to iptacopan. Please clarify the nature of these SAEs and the rationale for concluding that they were unrelated to iptacopan.

Causality of the three SAEs that led to discontinuation of iptacopan was assessed by the investigator, and these were classified as unrelated to iptacopan. The details regarding the three patients who discontinued iptacopan due to SAEs in the open-label extension study are presented below.¹⁷

- One patient discontinued iptacopan due to an SAE of renal impairment
- One patient discontinued iptacopan due to an SAE of C3G (post-transplant recurrent patient with C3G progression confirmed in kidney biopsy)
- One patient discontinued iptacopan due to an SAE of acute kidney injury from immune complex glomerulonephritis (post-transplant recurrent patient with several confounding

events leading to eGFR decline, none of which were suspected to be related to iptacopan by the investigator; the investigator suspected postinfectious, crescentic glomerulonephritis on top of not yet remitted C3G as the cause of the acute kidney injury)

A 14. The CS stated that one death was caused by cardiac arrhythmia but did not consider it to be related to iptacopan. Please clarify the details. Additionally, please also clarify any cardiovascular events reported, given the potential link between complement inhibition and thrombosis.

There was one death across the three iptacopan C3G studies, with the cause of death presumed to be cardiac arrhythmia that was not considered to be related to iptacopan by the study Investigator.¹⁷ A 24-year-old patient, originally in the Phase 2 Study, was found unresponsive and declared dead on Day 501. Post-mortem examination revealed no obvious cause of death.¹⁷ The evidence pointing to cardiac arrhythmia included arteriolar-nephrosclerosis, a clinical history of C3G, hypertension, focal myocardial scar, and a clinical history of hypocalcaemia.¹⁷ The patient had pre-existing conditions including anxiety, palpitations, and hyperparathyroidism. Possible confounders for the event included concomitant medications of methylphenidate (potential adverse drug reactions [ADRs] of tachycardia and arrhythmia), venlafaxine (potential ADRs of tachycardia and arrhythmia) as well as trazodone (warning for QT prolongation).¹⁷

The cardiovascular events reported in the broad safety set in the iptacopan clinical trials in C3G are presented in Table 11, though none of these were deemed to be related to iptacopan by the Investigator. Additionally, across the clinical studies included in the marketing authorisation application for iptacopan in its first indication (paroxysmal nocturnal haemoglobinuria [PNH]), no clinically meaningful abnormalities in cardiac safety-related assessments were observed.¹⁷

Table 11: Cardiovascular events (broad safety set)

Event	Number of patients in the broad safety set (N=101)	Severity	Relationship to iptacopan
SAEs			Not suspected to be related to iptacopan
Acute left ventricular failure	1	Moderate	
Atrial fibrillation	1	Moderate	
Pericarditis	1	Severe	
Cardiac failure	1	Moderate	
AEs			
Cardiomyopathy	1	Non-serious	

Abbreviations: AE, adverse event; SAE, serious adverse event.

Source: Novartis Data on File, 2024 (Summary of Clinical Safety in C3 glomerulopathy; v1.0 Table 2-5).¹⁷

Thrombosis is a frequent complication in paroxysmal nocturnal haemoglobinuria (PNH),¹⁸ and was therefore an AE of special interest (AESI) in the iptacopan clinical trial programme for PNH.¹⁹ The inclusion of thrombosis as an AESI was related to PNH as a disease, rather than a general risk associated with complement inhibition. Thrombosis was not an AESI in the iptacopan clinical trials in C3G, and no AEs of thrombosis were reported in patients receiving iptacopan (1 patient in the placebo arm had mild thrombosis during the double-blind period of APPEAR-C3G).⁹

Section B: Clarification on cost-effectiveness data

Patient population

B 1. Priority question. CS Table 33 provides an overview of baseline patient characteristics from APPEAR-C3G (used in CS base-case), pooled APPEAR-C3G and Phase 2 native kidney cohort (Cohort A) and RaDaR (registry data from patients with C3G in the UK). The RaDaR study indicated that the baseline patient characteristics in the APPEAR-C3G potentially do not accurately reflect UK clinical practice as the proportion of females in APPEAR-C3G is lower and the clinical characteristics (e.g. mean EGFR and CKD stage) do seem to reflect a healthier population in APPEAR-C3G.

- a) Please justify the use of the APPEAR-C3G patient characteristics in the CS base-case.

The base-case economic model used patient characteristics from APPEAR-C3G to be aligned with the source of clinical efficacy data used in the cost-effectiveness model.

A scenario analysis was conducted with patient characteristics from RaDaR,¹² using characteristics at time of diagnosis based on clinical experts' advice, since these were considered more reflective of future expected clinical practice where iptacopan would be initiated early in the disease course.⁴ This scenario resulted in a [REDACTED] % change in the ICER compared to the base case (full results are presented in Table 60 of the CS).

- b) Please elaborate on the generalisability of both the baseline risks and the relative effectiveness derived from APPEAR-C3G (e.g. as presented in CS Tables 34 and 35) to UK clinical practice.

UK clinicians confirmed that the patients included in APPEAR-C3G reflected patients who they considered would benefit from iptacopan in UK clinical practice and considered the trial data generalisable.⁴ Further information is provided in the response to clarification question A10.

- c) According to CS Table 7 (APPEAR-C3G baseline demographics and disease characteristics), there are significant imbalances between the two APPEAR-C3G arms (despite randomization and stratification). Please elaborate on the appropriateness of, and biases in both the baseline risks and the relative effectiveness derived from APPEAR-C3G (e.g. as presented in CS Tables 34 and 35) given these imbalances.

For details on the potential impact of baseline imbalances on clinical trial results, please refer to the response to question A8.

When it comes to use of APPEAR-C3G data in the economic model, it is important to note that only the eGFR slopes in option 1 of CS Table 34 (comparison iptacopan vs placebo based on 6-month double-blind period) would potentially be impacted by imbalances in baseline characteristics between groups. Patients in the iptacopan arm had notably higher proteinuria at baseline and exhibited a steeper pre-trial eGFR decline than the placebo arm, suggesting a more severe disease phenotype.^{4, 9} UK clinicians participating in an advisory board suggested that comparisons between the iptacopan and placebo groups may therefore underestimate the efficacy of iptacopan,⁴ and results of a post-hoc sensitivity analyses of the change from baseline in eGFR endpoint showed a larger treatment effect for iptacopan after adjusting for baseline UPCR (see response to question A8, Table 7).⁹ As such, cost-effectiveness analyses using eGFR slopes as in option 1 of CS Table 34 may bias against iptacopan and should be interpreted with caution.

eGFR slope options 2 (base-case) and 3 of CS Table 34 would not be impacted by imbalances in baseline characteristics between groups, since both the pre-iptacopan slope and the on-iptacopan slope were derived using data from *all* patients enrolled in APPEAR-C3G. The pre-iptacopan eGFR slope included historical and screening/run-in data from all APPEAR-C3G participants, and placebo data from the placebo arm patients. The on-iptacopan eGFR slope included data from the iptacopan arm of APPEAR-C3G, as well as data from the placebo arm after patients switched to iptacopan at the start of the open-label period. Therefore, baseline imbalances between the iptacopan and placebo arms of APPEAR-C3G do not affect the base-case economic analysis.

Model structure

B 2. Priority question. The model consists of 9 mutually exclusive health states: CKD stages 1-5 (separating between 3a and 3b), dialysis and post-transplant as well as death.

- a) The decision to use eGFR rather than reduction in proteinuria (UPCR) is justified by the lack of a robust surrogacy relationship for complement inhibitors. Please elaborate with supporting evidence on the quantitative surrogacy relationship between UPCR reduction and (long-term) clinical outcomes (such as eGFR decline, CKD progression, dialysis initiation, or mortality). i) specifically for complement inhibitors like iptacopan in C3G and, ii) in general in chronic kidney disease.

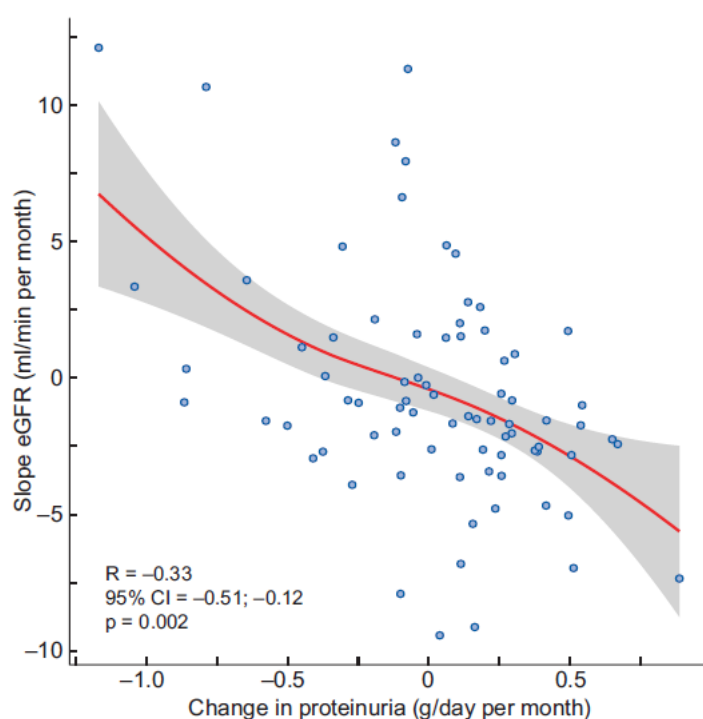
The model structure adopted for this submission follows well-established precedents, with health states in previous NICE TAs in chronic kidney diseases generally defined by CKD stages (unless other, non-kidney features of the respective disease prevailed) and KRT health states for dialysis and transplant (see CS Table 31). These health states were confirmed by UK clinicians to be relevant and key determinants of quality of life and costs in C3G.⁴

Given that CKD stages are defined by eGFR, use of eGFR trial data was considered the most direct approach to modelling disease progression,⁵ which is in alignment with the approach taken in several previous appraisals in other chronic kidney diseases (CS Table 31). Clinicians consulted during preparation of the clarification questions response reconfirmed that where

eGFR data is available, it should be used directly rather than predicted using surrogacy relationships.⁸

While evidence from observational and registry studies is generally aligned that a reduction in proteinuria is associated with a positive impact on longer-term outcomes in C3G, analysis methods and estimates of the quantitative relationship vary.²⁰⁻²³ For example, an analysis of RaDaR data found that a 50% reduction in UPCR from baseline to 12 months is associated with a reduced risk of kidney failure (compared to no UPCR reduction) with a hazard ratio (HR) of 0.33 (95% CI: 0.17, 0.63).²⁰ A published analysis of data from the Spanish GLOSEN registry concurred with the conclusion that a $\geq 50\%$ reduction in UPCR was significantly associated with a lower risk of kidney failure, but estimated a HR of 0.79 (95% CI: 0.56, 0.97; $p < 0.001$).²¹ The same study also found that there was an inverse relationship between the slope of eGFR and the change of proteinuria over time, reflected below in Figure 1, which supports that reduction in proteinuria positively impacts kidney function as measured by eGFR.²¹

Figure 1. Graphical representation of log change in eGFR as a function of log change in proteinuria



Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; p, p-value.

Source: Caravaca-Fontán et al. 2022 (Figure 3).²¹

Importantly, all currently available published evidence on the association of UPCR with eGFR and other clinical outcomes in C3G is based on UPCR reductions observed with currently used SoC treatments. As highlighted in the CS (see Section 1.3.5), these treatments do not address the underlying pathophysiology of C3G and predominantly constitute supportive care. On the other hand, iptacopan, as a Factor B complement inhibitor, is a targeted treatment for C3G. Clinicians consulted during preparation of the clarification questions response summarised that, for example, ACE inhibitors are considered as treating the consequences of CKD, whereas iptacopan, as a disease-modifying treatment, is considered as treating the cause of C3G.⁸ Therefore, clinicians considered it plausible that the long-term benefits of reducing UPCR with iptacopan could be greater than the long-term benefits of reducing UPCR with current SoC.⁸

Surrogate endpoint literature also warrants caution when it comes to transferring quantitative surrogacy relationships to other classes of treatments.²⁴ The NICE manual states that surrogate outcome validation is specific to the population and technology type under consideration (NICE manual section 4.6.8), and that extrapolation to a technology of a different class or with a different mechanism of action must be thoroughly justified (NICE manual section 4.6.9).²⁵ Given these circumstances, Novartis considers that prediction of eGFR or other clinical outcomes based on iptacopan UPCR data and surrogacy relationships from other classes of treatments would introduce undue uncertainty into the appraisal, especially since eGFR data are available from the iptacopan clinical trials in C3G and can be used in the economic model directly. This conclusion was supported by the consulted clinical experts.⁸

- b) Given that UPCR is the primary endpoint of APPEAR-C3G, please provide exploratory analyses assessing the potential correlation between UPCR reduction and eGFR decline. Similarly, please provide exploratory (survival) analyses illustrating the relationship between UPCR and CKD progression as well as between UPCR and dialysis initiation. Additionally, please provide analyses stratifying patients by UPCR response categories (e.g., $\geq 30\%$ vs. $< 30\%$ reduction from baseline) and comparing eGFR trajectories as well as dialysis-free survival.

An analysis was conducted to explore the potential correlation between change in UPCR and change in eGFR in APPEAR-C3G trial data. Please note that the analysis was only performed for the iptacopan arm, since for the placebo arm only six months of data were available. In participants randomised to the iptacopan arm, the exploratory analysis found a statistically significant correlation ($p = \blacksquare$) of change from baseline in eGFR at Month 12 with log-transformed change from baseline in UPCR at Month 6, with the correlation coefficient ($-\blacksquare$) indicating a moderate negative correlation.¹¹ While exploratory and limited by sample size and duration of follow-up, this analysis supports the association of UPCR reduction with benefit on eGFR.¹¹

CKD progression is defined by eGFR decline, therefore the result noted above provides information on the relationship between UPCR and CKD progression. No patients initiated dialysis during the 12-month duration of the APPEAR-C3G study and therefore an analysis of the relationship between UPCR and dialysis initiation was not feasible.

An analysis of eGFR trajectories stratified by UPCR response is shown in Table 12.¹¹ In the analysis of the 6-month double-blind treatment period of APPEAR-C3G, iptacopan treatment had a positive impact on eGFR decline compared to the pre-iptacopan eGFR slope both in patients with UPCR reduction $\geq 30\%$ and patients with UPCR reduction $< 30\%$. The effect size was larger (and statistically significant versus the pre-iptacopan eGFR slope) in patients with $\geq 30\%$ UPCR reduction.¹¹ The small number of patients in the placebo arm who had a UPCR reduction $\geq 30\%$ ($n=4$ of overall 36 patients) did not allow a meaningful analysis of eGFR slope stratified by UPCR reduction in the placebo arm.

In a further analysis of iptacopan arm patients after 12 months in APPEAR-C3G (double-blind + open-label period), similarly, iptacopan treatment had a positive impact on eGFR decline both in patients with UPCR reduction $\geq 30\%$ and $< 30\%$, but there was a larger magnitude of effect in patients with $\geq 30\%$ UPCR reduction.¹¹ In both UPCR responder groups, the change in eGFR slope versus the pre-iptacopan slope was statistically significant.¹¹

Overall, while exploratory and in a small sample size, these analyses suggest that greater reduction in UPCR with iptacopan may translate into greater eGFR benefit, although also lower reductions in UPCR (<30%) were associated with meaningful improvements in eGFR slope compared to the pre-iptacopan eGFR trajectory.

As noted above, no patients initiated dialysis and therefore an analysis of dialysis-free survival was not conducted.

Table 12. Model estimated eGFR (mL/min/1.73m²) slopes per year stratified by UPCR response (APPEAR-C3G exploratory analyses; FAS)

Treatment	Historical period eGFR slope per year (95% CI)	Double-blind period eGFR slope per year (95% CI)	Slope change per year (95% CI)	p-value
Patients with ≥30% reduction in UPCR from baseline to 6 months				
Iptacopan N=17	██████████	██████████	██████████	████
Placebo N=4	██████████	██████████	██████████	████
Difference	██████████	██████████	██████████	████
Patients with <30% reduction in UPCR from baseline to 6 months				
Iptacopan N=20	██████████	██████████	██████████	████
Placebo N=32	██████████	██████████	██████████	████
Difference	██████████	██████████	██████████	████
Treatment	Historical period eGFR slope per year (95% CI)	Double-blind + open-label period eGFR slope per year (95% CI)	Slope change per year (95% CI)	p-value
Patients randomised to iptacopan with ≥30% reduction in UPCR from baseline to 12 months				
Iptacopan N=21	██████████	██████████	██████████	████
Patients randomised to iptacopan with <30% reduction in UPCR from baseline to 12 months				
Iptacopan N=16	██████████	██████████	██████████	████

Footnotes: eGFR slopes per year were analysed using a linear mixed effects model including time (analysis day before or after change point (day 1 of iptacopan treatment)) as a continuous covariate, participant-level intercept and slope (time) as random effects. Intercurrent events were handled with a treatment policy strategy.

Source: Novartis Data on File. 2025. (Clarification questions supplementary analyses – Section B2).¹¹

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; UPCR, urine protein to creatinine ratio.

- c) Please provide a model structure and scenario analyses using the primary endpoint of APPEAR-C3G, i.e. UPCR to define health states (pre-KRT).

As noted in the response to question B2 a), the CKD stage-based model structure adopted for this submission follows precedents established by multiple previous NICE TAs (see CS Table 31). The utilised health states were confirmed by UK clinicians to be relevant and key determinants of quality of life and costs in C3G.⁴

Defining health states by UPCR levels would deviate from previous models used in various other chronic kidney diseases. In addition to this request requiring a complete restructure or rebuild of the submitted model, parameterisation of the model would be challenging, with various required model inputs (e.g. for mortality) generally published by CKD stage and not by UPCR levels.

Reduction in UPCR is a meaningful trial endpoint and useful to see treatment effect within a short time frame both in a trial setting and clinical practice,⁴ but from a clinical perspective, clinicians confirmed that eGFR is the most important outcome to monitor longer-term, as a measure of kidney function.⁸ In addition, since KRT is not started based on UPCR levels but based on low eGFR indicating kidney failure, a model using UPCR-based health states pre-KRT would still need to also track eGFR in order to correctly model the start of KRT.

Due to these reasons, no alternative model structure and scenario analyses have been provided. In case we should have misunderstood the EAG's request and this related to modelling eGFR decline based on a UPCR surrogacy relationship, we refer to our response to question B2 a).

- d) Please justify why a different model structure was used compared with previous NICE TAs, for instance in TA358 (considering tolvaptan): i) CKD stages 3a and 3b were not separated and; ii) KRT could consist of conservative care (management to prolong kidney function and control symptoms of ESRD), haemodialysis (HD; either hospital HD, satellite HD or home HD), peritoneal dialysis (PD; either ambulatory or continuous ambulatory PD) or kidney transplantation (either from a living or deceased donor). The TA358 model allows for different KRT in subsequent cycles (although switching between dialysis modalities was not possible).

i) While TA358 combined CKD stages 3a and 3b,²⁶ several other TAs separated these states. As noted in Table 31 of the CS, TA942, TA937, TA775 and TA599 included CKD stages 3a and 3b as distinct states,²⁷⁻³⁰ while TA882 grouped stages 1–3a and 3b–4.³¹ Separating CKD stages 3a and 3b aligns with KDIGO and NICE guidance on CKD staging,^{32, 33} and provides additional granularity to the economic modelling.

ii) As noted on page 105 of the CS, given the young average age at kidney failure, UK clinicians advised that all patients with C3G would be expected to commence KRT following kidney failure, with no patients receiving conservative management instead.⁴ As such, conservative care was not considered an appropriate treatment and not included in the model.

Within the KRT health state, patients are separated into dialysis and post-transplant. When receiving dialysis, the model accounts for the receipt of different types of dialysis for both utilities

and costs. For the dialysis utility in the economic model, a weighted average was calculated according to the proportion of patients receiving each type of dialysis, sourced from a RaDaR analysis in patients with C3G (HD: 85.3%; PD: 14.7% [APD: 11.8%, CAPD: 2.9%]).¹² The cost of dialysis was calculated using NHS reference costs, with HD assumed to be repeated three times per week and continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) assumed to be carried out daily.³⁴⁻³⁶ Within the calculation of HD costs, hospital, satellite, and home HD were weighted by total activity for the respective HRG codes in the NHS reference costs. Costs for HD, CAPD and APD were then weighted for calculation of the average dialysis cost, with proportions again based on RaDaR data in patients with C3G.¹²

The cost of kidney transplant in the model also considers both living or deceased donor transplantations, again as a weighted average based on the proportions in RaDaR (living donor: 34.2%; deceased donor: 65.8%).¹² Details of the cost calculations for dialysis and transplant are provided in Table 50 of the CS.

As with TA358, the model in this submission allows for different types of KRT in subsequent cycles. Patients on dialysis have a per-cycle probability of receiving a transplant in each cycle, while transplanted patients have a per-cycle probability of experiencing graft failure in each cycle, requiring a return to dialysis (see CS Section 3.3.2.2). The model allows for multiple transplants with multiple instances of graft failure over the time horizon, reflecting a common cycle of transplant and dialysis as experienced by patients with C3G (please also refer to the response to question B4).^{4, 12, 37}

e) In the CS it is stated that:

- *“A 3-month cycle length was considered to provide sufficient detail to capture the impact on costs and QALYs as patients progressed through the model”*
- *“Aligned with prior appraisals in other chronic kidney diseases (Table 31) which included cycle lengths ranging from 4 weeks–1 year”*

Please provide additional justification why a 3-month cycle length is considered sufficiently short (rather than 1 month/4 weeks as used in TA599, TA623, TA775, TA825, TA890 and TA937) to capture the impact on costs and QALYs as patients progressed through the model.

While several previous appraisals used a shorter cycle length, it should be noted that this may have in some cases been driven by other features of the respective disease (e.g. pruritus in TA890 or hyperkalaemia in TA599 or TA623). Among the 13 appraisals identified in the TLR, five used a cycle length longer than 3 months, up to 1 year (see CS Table 31).

In the case of C3G, with the modelled eGFR decline, a three-month cycle length was considered sufficiently short to capture the impact on costs and QALYs, ensuring that patients sequentially progress through each CKD stage (without skipping CKD stages). From a clinical perspective, a three-month cycle length aligns with recommendations that the presence or progression of CKD should be confirmed based on eGFR measurements taken across a time period of at least 3 months.^{33 38} Therefore, a three-month cycle length was considered appropriate.

B 3. KRT initiation was assumed to be at eGFR ≤ 7.6 mL/min/1.73 m² (as stated in CS Table 36), which is lower than the standard CKD Stage 5 threshold of <15 mL/min/1.73 m² (as stated below CS Figure 27).

- a) What is the clinical rationale for this specific threshold for KRT initiation (of ≤ 7.6 mL/min/1.73 m²)?

The threshold for KRT initiation used in the economic model base case was derived as a weighted average of eGFR values at time of dialysis initiation or receipt of a pre-emptive transplant, based on UK Renal Registry data (see Section 3.3.2.2 of the CS). The UK Renal Registry, which collects and reports data annually on approximately 70,000 people receiving KRT in the UK, reports that dialysis was on average started at an eGFR value of approximately 7 mL/min/1.73 m², while pre-emptive (without first receiving dialysis) transplants took place at an eGFR of approximately 10 mL/min/1.73 m².³⁹ These values were in line with estimates from UK clinicians in the C3G advisory board.⁴ For the economic model base case, the threshold to start KRT at an eGFR of 7.6 mL/min/1.73 m² was derived as a weighted average of the above values, accounting for 18.4% of UK patients with C3G receiving a pre-emptive transplant as their first KRT modality, based on RaDaR data.¹² The KRT threshold value used in the base case was confirmed to be reasonable by a UK clinical expert.⁵

A scenario analysis presented in the CS set the KRT threshold value to 10 mL/min/1.73 m², representing the average eGFR value at receipt of a pre-emptive transplant.³⁹ Further scenario analyses are presented in response to question B3 c) (Table 13), showing a limited impact of variation of the KRT threshold on cost-effectiveness results.

- b) Please justify why a different threshold was used compared with previous NICE TAs, for instance in TA358 (considering tolvaptan) KRT would start at eGFR <8.5 mL/min/1.73 m².

TA358 used data specific to the indication under assessment, i.e. autosomal dominant polycystic kidney disease, based on a publication from 2014.^{26, 40} The threshold used in the CS for iptacopan in C3G was derived as a weighted average based on the latest available UK Renal Registry data from 2022, for patients with CKD overall.³⁹ The threshold used within the CS is thus based on the most recent available data from the UK, and while not C3G-specific, UK clinicians with experience in treating patients with C3G confirmed that the values used in the calculation and the resulting threshold value were appropriate.^{4, 5} Scenario analyses showed a limited impact of variation of the KRT threshold on cost-effectiveness results (see response to question B3 c), Table 13).

- c) Please provide an updated economic model and scenario analyses assuming eGFR values of 5 mL/min/1.73 m² and 7 mL/min/1.73 m² (or the midpoint of 6 mL/min/1.73 m²) as the threshold for KRT initiation, in line with NICE guideline NG107 which recommends starting replacement therapy “around 5 to 7 mL/min/1.73 m²”.

Please note that the recommendation in NICE guideline NG107 relates specifically to starting *dialysis*, rather than KRT more broadly: “1.1.2 Consider starting dialysis when indicated by the impact of symptoms of uraemia on daily living, or biochemical measures or uncontrollable fluid

overload, or at an estimated glomerular filtration rate (eGFR) of around 5 to 7 mL/min/1.73 m² if there are no symptoms.”⁴¹ Based on the above, NICE guideline NG107 recommends starting dialysis at an eGFR of around 5 to 7 mL/min/1.73 m² if the person has no symptoms, or earlier (at a higher eGFR value) if symptoms require it.⁴¹

Pre-emptive transplants, however, regularly take place at a higher eGFR value, as confirmed both by UK Renal Registry data (eGFR of approximately 10 mL/min/1.73 m²)³⁹ and UK clinicians treating patients with C3G.⁴ Since the KRT threshold within the economic model is applied to all forms of KRT, the base case threshold value was derived as a weighted average of eGFR values for initiation of dialysis and receipt of a pre-emptive transplant (see response to question B3 a)). Based on the clinical advice received during preparation of the CS, a KRT threshold value of 7.6 mL/min/1.73 m² is considered the most appropriate for use within the model base case.^{4, 5}

The impact of changing the KRT threshold value is explored in Table 13, including the additional scenario analyses requested by the EAG, overall demonstrating that variation of the KRT threshold has limited impact on cost-effectiveness results (range of ICER change: [REDACTED] % to [REDACTED] %). Please note that all cost-effectiveness results presented in this document are based on a revised company base case which accounts for drug wastage, as further explained in the response to question B15.

The economic model included with the CS provides functionality to flexibly amend the KRT threshold value, by entering alternative values in cell D62 of the Clinical data tab.

Table 13: Scenario analysis results: Alternative KRT threshold values

KRT Threshold	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			% change in ICER (versus revised base case)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	
Revised company base case								
KRT threshold of eGFR ≤7.6 mL/min/1.73m²	██████	16.88	£355,162	15.13	██████	1.74	██████	N/A
Scenario analysis within the company submission (using revised model)								
KRT threshold of eGFR ≤10 mL/min/1.73m²	██████	16.83	£361,145	15.09	██████	1.74	██████	██████
Scenario analyses as requested by the EAG								
KRT threshold of eGFR ≤5 mL/min/1.73m²	██████	16.92	£349,004	15.18	██████	1.74	██████	██████
KRT threshold of eGFR ≤6 mL/min/1.73m²	██████	16.90	£351,405	15.16	██████	1.74	██████	██████
KRT threshold of eGFR ≤7 mL/min/1.73m²	██████	16.89	£353,822	15.14	██████	1.74	██████	██████

Abbreviations: eGFR: estimated glomerular filtration rate; ICER: incremental cost-effectiveness ratio, KRT: kidney replacement therapy; QALY: quality adjusted life year.

- d) In clinical practice some patients may start KRT at different eGFR values due to complications or comorbidities. Please explain whether and how this was implemented/considered in the economic model.

As noted in response to question B3 a), the KRT threshold was derived from mean eGFR values at initiation of dialysis or receipt of a pre-emptive transplant, respectively, as reported in UK Renal Registry data.³⁹ Variation between individuals starting KRT is assumed to already be considered within these values.

Variation of the KRT threshold in scenario analyses was seen to have limited impact on cost-effectiveness results (Table 13). Please note that the updated economic model submitted with the clarification questions response now also considers the KRT threshold as a parameter in both the deterministic and probabilistic sensitivity analysis. As shown in Figure 18, the KRT threshold was not within the top 10 most influential parameters on the ICER within the DSA therefore is not considered a key model driver.

- e) Various assumptions related to KRT were based on data from RaDaR, e.g. the percentage of patients receiving a pre-emptive transplant, the median time from dialysis to transplant and the median time to graft failure. The percentage of patients ineligible for a transplant were informed by Adelphi DSP survey data. Please justify why these assumptions were not informed by data from the clinical trials and provide an updated economic model and scenario analysis doing so.

Given that most patients enrolled in APPEAR-C3G were in early stages of the disease, no meaningful clinical trial data are available to inform KRT inputs in the economic model.

Parameters relating to dialysis and transplant are also highly specific to geography, with availability of donor organs, transplant protocols, wait times etc. all likely to vary from country to country. Consequently, use of data from the UK was considered most appropriate for economic modelling. RaDaR provides UK-specific data on KRT and time to graft failure in a C3G population,¹² is thus highly relevant to this submission, and was supported by a UK clinical expert as suitable source for these model inputs.⁵ Data on transplant ineligibility was sourced from Adelphi DSP survey data, in the absence of RaDaR data, and varied in a scenario analysis presented in the CS, accounting for feedback received from UK clinicians (see CS, Sections 3.3.2.2 and 3.10.3).

Since no clinical trial data are available for these parameters, no additional scenario analysis is provided.

- f) Please elaborate on the implications of the responses to the preceding sub-questions.

The implications of the responses to the preceding sub-questions have been noted as part of the relevant responses themselves; please see above.

- g) According to the CS : *“people in the SoC arm receiving on average 1.9 transplants over their lifetime, which a UK clinical expert considered plausible”*. Please provide

evidence (in addition to expert opinion) supporting the plausibility of this estimate. Moreover, please provide the average number of transplants for iptacopan and elaborate on the plausibility of this estimate.

C3G commonly recurs following kidney transplantation, with recurrence rates reported in the literature to be between 55–85%, with a median time to recurrence of 14–28 months.⁴²⁻⁴⁸ It is therefore expected that many patients experience graft failure (the median time from transplant to graft failure based on RaDaR data was 6.5 years),¹² and so may receive multiple transplants (please also note the response to question B4 further below).

Amongst C3G prevalent RaDaR patients (n=240), 61 patients had received one transplant, 12 patients had received two transplants, and 2 patients had received three or more transplants, at latest follow up.¹² However, this is a cross-sectional study, and given the young average age of the prevalent population (age at latest follow-up: mean [SD] 44.7 [21.3]; median [IQR] 42.8 [25.7, 63.8]) and short median time to graft failure as observed in RaDaR data,¹² it is therefore expected that some patients may receive further transplants during their lifetime. The average number of 1.9 transplants per patient over a lifetime in the SoC arm of the economic model was confirmed as a plausible prediction by clinical experts.^{5, 8}

The average number of transplants per patient over a lifetime in the iptacopan arm of the model (base case) is predicted as 1.46 transplants. A reduction in the mean number of transplants in the iptacopan arm compared with the SoC arm of the model was considered clinically plausible by experts, given that eGFR data from the APPEAR-C3G trial and its extension study suggested that iptacopan is able to slow the progression of C3G in a meaningful way.^{4, 8, 10} By slowing the progression of C3G, iptacopan is expected to reduce the number of patients experiencing kidney failure, thereby reducing the number of patients requiring a transplant or dialysis.⁸ However, clinical experts found it difficult to comment on the specific value of 1.46 transplants over a lifetime, also considering that the iptacopan arm in the model contains patients on iptacopan as well as patients who discontinued iptacopan during the model time horizon and subsequently receive SoC alone.⁸ To further test the model's sensitivity to variation of transplant model parameters, additional scenario analyses were conducted, which are presented in the response to clarification question B4 a).

h) CS Table 36 provides KRT input parameters used in the CS base-case:

- eGFR threshold for starting KRT: 7.6 mL/min/1.73 m²
- Patients ineligible for a kidney transplant: 16.8%
- Assumed maximum age for receipt of transplant: 80 years
- Patients receiving a pre-emptive transplant as their first KRT modality: 18.4%
- Median time from start of dialysis to transplant (excluding patients receiving a pre-emptive transplant): 1.9 years (8.7% probability per 3-month cycle of receiving a transplant)

- Median time from transplant to graft failure: 6.5 years (2.6% probability per 3-month cycle of having graft failure)

Please justify per input parameter whether it is clinically plausible according to expert opinion and provide supporting evidence.

- The source and derivation of the KRT threshold are outlined in response to question B3 a). The eGFR threshold for KRT was first discussed as part of a UK clinical advisory board.⁴ As kidney failure is defined as eGFR <15 mL/min/1.73 m², an early draft of the economic model initially assumed that KRT would be started at that point, but clinical advisors stated that in practice KRT would only be started at a lower eGFR value.⁴ In response to these discussions, the model was amended accordingly and a value of 7.6 mL/min/1.73 m² was derived from Renal Registry data as KRT threshold (see response to question B3 a)). This value was confirmed as plausible in further discussions with a clinical experts, who also highlighted the strength of the Renal Registry as a source^{5, 8}
- The value for transplant ineligibility is derived from C3G-specific Adelphi DSP survey data from the EU4 and the UK, which indicated that among 107 people with C3G in need of a transplant, 18 (16.8%) were considered ineligible to receive a transplant.⁴⁹ The proposed value of 16.8% of people being ineligible for a transplant was discussed during the aforementioned clinical advisory board.⁴ Clinical experts commented that this value seemed high when considering ineligibility for a first transplant, however that the ineligible proportion of patients would increase for subsequent transplants.⁴ This was further confirmed by a subsequent expert discussion, who explained that with increasing age, patients may develop more comorbidities and become more sensitised and thus ineligible for a transplant.⁵ Therefore, a scenario analysis was included in the CS, assuming that 6.8% were ineligible for a first and 26.8% for a subsequent transplant (reflecting base case value +/- 10%, respectively), with minor impact on the ICER (██████ using the updated model; see Table 51)
- The maximum age for receipt of a transplant was assumed as 80 years in line with NICE TA942 in CKD;²⁷ while this value was not specifically discussed with clinical experts due to time constraints, this precedent supports the clinical plausibility of this assumption. In order to examine the effect of this limit, a scenario analysis explored having no age limit, which had a negligible effect on the ICER (██████; see Table 51)
- The number of patients receiving a pre-emptive transplant, median time from dialysis to transplant, and median time from transplant to graft failure were based on the C3G cohort in RaDaR,¹² and are therefore both UK- and C3G-specific, making these values highly plausible as model inputs. Clinical experts expressed support for the use of RaDaR inputs to inform modelling during conversations,^{4, 8} and advisors further confirmed that the values used in the model were clinically plausible^{5, 8}

B 4. The economic model allows for multiple transplants with graft failure leading back to dialysis

- a) Please justify the assumption of repeated transplant, and whether this is consistent with clinical practice? Please also elaborate whether it would be more appropriate to cap the maximum number of graft failures and transplants?

The assumption that some people with C3G will require multiple transplants over their lifetime is consistent with clinical practice, as kidney transplantation does not address the underlying pathophysiology of C3G. C3G recurrence rates post-transplantation have been reported as 55–85%, with a median time to recurrence of 14–28 months following transplantation.⁴²⁻⁴⁸ As a consequence of C3G recurrence, the risk of graft failure in C3G is high, with reported graft failure rates of 50% among patients with disease recurrence, and a median time from transplant to graft failure of 77 months.⁴⁸ Similarly, RaDaR data from patients with C3G indicates a median time from first transplant to graft failure of 6.5 years (95% CI: 3.0, 8.1).¹² Following graft failure, patients are required to either return to dialysis or receive another kidney transplant. In RaDaR data, among 75 prevalent kidney transplant recipients with C3G, 14 (18.7%) had received two or more kidney transplants at the time of analysis;¹² given the young median age of the prevalent cohort (36.4 years) and short median time to graft failure (6.5 years), it is likely that several additional patients will receive more transplants over their lifetime.

UK clinicians consulted during the preparation of the clarification questions response confirmed that patients with C3G commonly receive multiple transplants, given the young age at diagnosis and rapid progression to kidney failure.⁸ They further advised that from a clinical perspective, it is not appropriate to cap the number of transplants a person with C3G may receive.⁸

While they confirmed that an average of 1.9 transplants in the SoC arm over a patient's lifetime, as predicted by the model, was plausible (see response to question B3 g) above), they recommended to check model predictions in terms of what proportion of patients received 3 or more transplants, and what was the maximum.⁸ However, it was not possible to perform this check given the memoryless nature of a Markov cohort model structure.

Therefore, two additional scenarios have been included to investigate the impact of a lower number of transplants on cost-effectiveness results (see Table 14). In the model base case, patients in the SoC arm receive on average 1.9 transplants over a lifetime. In one scenario, the percentage of patients eligible for a subsequent transplant was reduced from 83.18% in the base case to a value of 63.89% (cell D55 of the 'Clinical data' tab) to yield an average of 1.5 transplants in the SoC arm. (Please note that a calculation of the average number of transplants within the SoC arm has been added to the economic model and can be found in cell AI12 on the 'SoC' tab of the model.) This scenario reduced the ICER (■■■■). In another scenario, transplants were effectively capped at 1, by setting the percentage of patients eligible for a subsequent transplant to 0%. This scenario reduced the ICER further (■■■■ vs base case). These scenario analyses demonstrate that if the average number of transplants received by patients on SoC was lower in clinical practice than predicted in the model base case, the model base case overestimates the ICER of iptacopan compared with SoC alone. All scenario analyses relating to transplant inputs are summarised in the response to question B4 d).

b) How is the probability of repeated transplant estimated?

Using RaDaR data from patients with C3G indicating a median time to graft failure post-transplant of 6.5 years,¹² a per cycle probability of graft failure of 2.6% was calculated and included in the model (see calculation in row 59 of the 'Clinical data' tab). Following graft failure, it was assumed that a proportion of patients were no longer eligible for transplantation; in the base case, this was assumed to be same as the proportion that were ineligible for a first transplant (16.8%; input as 83.18% eligible for a subsequent transplant in cell D55 of the 'Clinical data' tab). Subsequently, the per-cycle transplant probability of 8.7% (derived from RaDaR data from patients with C3G indicating a median time to transplant [excluding pre-emptive transplants]

of 1.9 years;¹² see calculation in row 58 of the 'Clinical data' tab) was applied to the transplant eligible patients.

- c) Is there a distinction between early versus late graft failure in terms of transition probabilities? Please justify why (not)?

While early graft failure is driven by acute rejection, graft failure in C3G also commonly occurs later on, due to the high rate of disease recurrence following transplantation. Details are provided in the CS, Section 1.3.4.5. Given the memoryless nature of a Markov cohort model structure which does not allow tracking time since receipt of a transplant for an individual patient, it was not possible to incorporate time-varying graft failure rates in the economic model.

The median time to graft failure (point estimate 6.5 years) was varied in the deterministic sensitivity analysis (DSA) in line with the 95% CI values of the RaDaR analysis (3.0–8.1), with the impact on the ICER shown in Figure 31 of the CS. An updated tornado plot, incorporating the revised base case (see response to question B15) and updated DSA inputs, is presented in the response to question B22 (Figure 18).

- d) Please elaborate on the implications of the responses to the preceding sub-questions.

Table 14 presents results of all scenario analyses which vary transplant eligibility inputs. Along with new scenarios described in the response to question B4 b), the table also reflects a scenario included in the CS. This scenario was based on feedback from UK clinicians that the proportion of patients ineligible for a first transplant may be lower and the proportion ineligible for a subsequent transplant may be higher, given that with increasing age, they may develop more comorbidities and become more sensitised.^{4, 5} Therefore, a scenario analysis included in Section 3.10.3 of the CS assumed that 6.8% were ineligible for a first and 26.8% for a subsequent transplant (reflecting base case value +/- 10%, respectively).

Table 14: Scenario analysis results: Alternative transplant eligibility inputs

Scenario	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			% change in ICER versus company base case
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	
Revised company base case (transplant eligibility of 83.2% for initial and subsequent transplants)	██████	16.88	£355,162	15.13	██████	1.74	██████	██████
Scenario analysis within the company submission (using revised model): transplant eligibility of 93.18% for initial and 73.18% for subsequent transplants	██████	16.91	£355,643	15.18	██████	1.73	██████	██████
New scenario analysis 1: transplant eligibility of 63.89% for subsequent transplants	██████	16.78	£385,613	14.94	██████	1.85	██████	██████
New scenario analysis 2: transplant eligibility of 0% for subsequent transplants (i.e. capped at maximum of 1 transplant)	██████	16.58	£449,492	14.52	██████	2.06	██████	██████

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; SAE, serious adverse event; QALY, quality adjusted life year.

Intervention technology and comparators

B 5. The comparator is SoC alone, which may include ACEi (ramipril; 47.3%), ARB (losartan; 52.7%), CS (prednisolone; 32.4%), MMF (36.5%), and SGLT2ni (dapagliflozin; 5.4%). The exact treatment regimens are modelled as components of the SoC basket, along with the proportion of patients receiving each component.

- a) Please clarify and justify whether these proportions are fixed over time, or whether they change over time (e.g. are patients allowed to switch between SoC treatments during disease progression)?

As SoC is modelled as a single comparator comprising a basket of treatments, patients do not switch between individual SoC treatments over the model time horizon. The proportion of patients receiving each component of SoC was sourced from participant characteristics at baseline in APPEAR-C3G, and was assumed equal in the iptacopan and comparator arms.⁹ The proportions were considered broadly reflective of UK clinical practice by clinical experts, except for SGLT2is,⁴ which were therefore varied in a scenario analysis, resulting in a negligible increase of the ICER (■■■■); see Table 51).

The proportions of patients on the individual SoC components were fixed in the model over time (until start of KRT, see below). This is in line with the APPEAR-C3G protocol requiring patients to remain on a stable dose of their SoC background medications throughout the trial. Therefore, the modelling of SoC aligns with the trial data which informed model inputs for disease progression.

When patients start KRT, all components of the SoC basket were assumed to be discontinued except for ACEi/ARB, since UK clinicians were aligned that these treatments would usually be continued while on KRT, due to their blood pressure-lowering effects.^{4, 50}

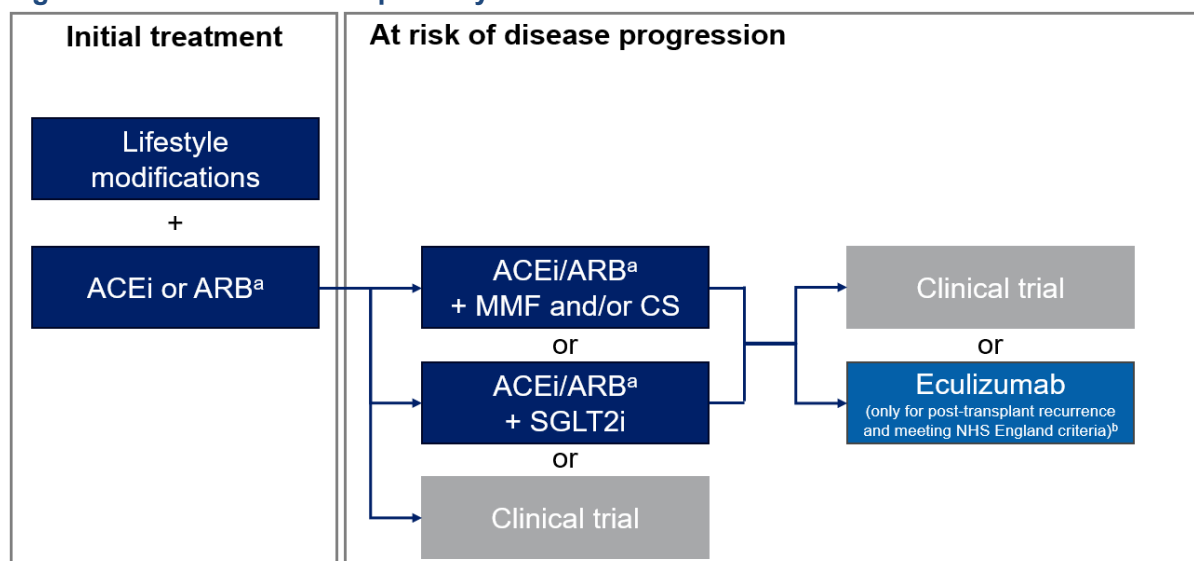
- b) Please clarify and justify whether patients can receive multiple SoC treatments simultaneously? Or monotherapy? For example, can a patient be on both an ACEi (e.g. ramipril) and an ARB (e.g. losartan)?

Patients can receive multiple SoC treatments simultaneously, aligning with the current treatment pathway for C3G in the UK, presented in the CS (Figure 3) and reproduced below in Figure 2.

Regarding ACEi and ARB use, guidelines generally recommend the use of one or the other.^{33, 51} KDIGO guidelines note that these treatments have been used in combination in diabetic patients, however with uncertainty surrounding the efficacy and potential for increased risk of adverse events.⁵¹ In APPEAR-C3G, two patients (2.7%) received both an ACEi and an ARB simultaneously.⁹

Given that the proportion of patients on each component of SoC background medication was assumed equal in the iptacopan and comparator arms of the model – reflecting the comparison of ‘iptacopan + SoC’ vs ‘SoC alone’ – adjustments to the proportion of treatments are expected to have a minimal effect on cost-effectiveness results. Overall, the SoC arm of the model is considered to provide a good representation of the use of the components of SoC in UK clinical practice (also see response to question B5 a) above).

Figure 2: Current treatment pathway for C3G in the UK



^aTo a maximally tolerated licensed dose, unless intolerant or contraindicated. ^bOnly a very small number of patients with highly aggressive post-transplant recurrence of C3G qualify for treatment with eculizumab under the NHS England commissioning policy.¹

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C3G, complement 3 glomerulopathy; CS, corticosteroids; MMF, mycophenolate mofetil; NHS, National Health Service; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

- c) If patients can receive multiple SoC treatments simultaneously, please clarify and justify how the combined treatment effect is accounted in the economic model?

eGFR slopes informing effectiveness for SoC alone and iptacopan + SoC are derived from data in the APPEAR-C3G population, which included simultaneous use of multiple SoC treatments in a proportion of patients (see response to question B5 a) above). Therefore, the modelled clinical effectiveness of SoC accounts for the receipt of multiple SoC treatments simultaneously and provides an accurate representation of the combined treatment effect of SoC.

- d) Please clarify and justify how the effectiveness of each SoC treatment is estimated.
In case patients can receive multiple SoC treatments simultaneously, are treatment effects considered additive or how is the combined treatment effect (of multiple SoC components) estimated in the economic model?

As noted in response to question B5c, effectiveness (rate of eGFR decline) is modelled for the SoC basket as a whole, thereby reflecting combined treatment effects as applicable.

- e) Please elaborate on the implications of the responses to the preceding sub-questions.

The implications of the responses to the preceding sub-questions have been noted as part of the relevant responses themselves; please see above.

B 6. Please include, consistent with the final scope, eculizumab as a comparator in the economic model for people who have previously had a kidney transplant and who have highly aggressive C3 glomerulopathy recurrence as specified in the NHS England clinical commissioning policy for eculizumab.

Please refer to the responses to clarification questions A3 and A11.

Treatment effectiveness

B 7. Priority question. Disease progression was modelled based on eGFR slope data from the iptacopan clinical trials in C3G.

- a) Please provide step-by-step details of how the eGFR slopes reported in Table 34 of the CS were calculated for all three options.

Option 1. eGFR slope change analysis APPEAR-C3G by treatment group: historical data + APPEAR-C3G double-blind period

Data from the historical period and the 6-month double-blind period of APPEAR-C3G were used for this analysis. The analysis was carried out using a linear mixed effects model including treatment as a factor and time (analysis day from randomisation)/time after change point as a continuous covariate. The treatment by time interaction was fitted as fixed effect. Participant-level intercept and slope (time) was included in the model as random effects allowing the intercept and the slope to vary for each participant. The mean (95% CI) pre- and post-treatment slopes and the slope change (95% CI) were provided by treatment group, as well as for the difference between iptacopan and placebo groups. The eGFR slope change analysis can be written algebraically as follows:

$$Y_{ij} = \alpha_{PBO} + \beta_{PBO}t_{ij} + \beta_{PBOchange}t_{ij}^* + (\alpha_{diff} + \beta_{diff}t_{ij} + \beta_{diffchange}t_{ij}^*)z_j + u_{0j} + u_{1j}t_{ij} + u_{2j}t_{ij}^* + e_{ij}$$

Where:

- Y_{ij} is the eGFR measurement at the i th timepoint for participant j
- α_{PBO} and α_{diff} are the intercepts (representing initial eGFR value at baseline) for the placebo group and the difference between iptacopan and placebo groups
- β_{PBO} and β_{diff} are the pre-treatment slope for the placebo group and the difference between iptacopan and placebo groups
- $\beta_{PBOchange}$ and $\beta_{diffchange}$ are the slope change (i.e. post-treatment slope – pre-treatment slope) for the placebo group and the difference between iptacopan and placebo groups
- t_{ij} is the i th time for participant j (in days). $t_{ij} \leq 0$ represents the pre-treatment period whilst $t_{ij} > 0$ represents the post-treatment period
- $t_{ij}^* = t_{ij}I(t_{ij} > 0)$ represents the i th time for participant j after treatment (before treatment $t_{ij}^* = 0$; after treatment $t_{ij}^* = t_{ij}$)

- z_j is the randomized treatment group (1 = iptacopan; 0 = placebo)
- u_{0j}, u_{1j}, u_{2j} represent the participant-level random effects terms and follow a multivariate normal distribution with mean 0 and diagonal covariance matrix
- e_{ij} is the residual error

Please note that only the eGFR slopes generated for the double-blind period ('post-treatment period') were used in the economic model (scenario analysis), with the placebo arm slope used for the SoC arm and the iptacopan arm slope used for the iptacopan arm in the model.

Option 2. eGFR combined slope change analysis using APPEAR-C3G and open-label extension study data: historical data + APPEAR-C3G double-blind period + APPEAR-C3G open-label period + open-label extension study (patients from APPEAR-C3G only)

Historical data and data from the 6-month double-blind period of APPEAR-C3G, 6-month open-label period of APPEAR-C3G, and open-label extension study were used for this analysis. Data from patients randomised to the iptacopan group were combined with data from patients randomised to the placebo group; the placebo group 6-month double-blind data were considered as pre-iptacopan data, while placebo group 6-month open-label data (after switch to iptacopan) were considered as post-iptacopan data. A generalised linear mixed effects model with a common intercept, a pre-iptacopan treatment slope, and a post-iptacopan treatment slope was used to estimate the pre-/post-iptacopan slopes. The eGFR combined slope change analysis can be written algebraically as follows:

$$Y_{ij} = \alpha + \beta_{pre}t_{ij} + \beta_{change}t_{ij}^* + u_{0j} + u_{1j}t_{ij} + u_{2j}t_{ij}^* + e_{ij}$$

Where:

- Y_{ij} is the eGFR measurement at the i th timepoint for participant j .
- α is the common intercept (representing initial eGFR value at baseline).
- β_{pre} is the pre-iptacopan treatment slope.
- β_{change} is the slope change (i.e. post-iptacopan treatment slope – pre-iptacopan treatment slope).
- t_{ij} is the i th time for participant j (in days). $t_{ij} \leq 0$ represents the pre-iptacopan treatment period whilst $t_{ij} > 0$ represents the post-iptacopan treatment period.
- $t_{ij}^* = t_{ij}I(t_{ij} > 0)$ represents the i th time for participant j after iptacopan treatment (before iptacopan treatment $t_{ij}^* = 0$; after iptacopan treatment $t_{ij}^* = t_{ij}$).
- u_{0j}, u_{1j}, u_{2j} represent the participant-level random effects terms and follow a multivariate normal distribution with mean 0 and diagonal covariance matrix.
- e_{ij} is the residual error.

The model allowed the intercept and slope to vary for each participant.

In the economic model (base case), the pre-iptacopan slope was used to inform the SoC arm, while the post-iptacopan slope was used to inform the iptacopan arm in the model.

Option 3. eGFR combined slope change analysis using pooled C3G data: historical data + APPEAR-C3G double-blind period + APPEAR-C3G open-label period + Phase 2 Cohort A data + open-label extension study (patients from APPEAR-C3G and Phase 2 Cohort A)

The analysis used the same model as in 2 above but included additional data from Cohort A from the Phase 2 study and the open-label extension.

In the economic model (scenario analysis), the pre-iptacopan slope was used to inform the SoC arm, while the post-iptacopan slope was used to inform the iptacopan arm in the model.

- b) Please provide step-by-step details of how the rates and probabilities of progression to the next state reported in Table 35 of the CS were calculated.

The rates and probabilities of progression to the next state are based on the annual rate of eGFR progression for both the iptacopan and SoC arms, taken from Table 35 of the CS (in the base case: annual eGFR slope of $-7.224 \text{ mL/min/1.73 m}^2/\text{year}$ for SoC and $-0.289 \text{ mL/min/1.73 m}^2/\text{year}$ for iptacopan).

As noted on page 103 of the CS, the time to move between states was defined as the time taken for eGFR to decline from the midpoint of the current CKD stage to the midpoint of the following stage. This approach assumes a uniform distribution of patients across a CKD stage and was used in the base case following validation with clinical and health economics experts.⁵ The difference between midpoints was divided by the annual rate of eGFR progression to give the time to next state. The rate of progression was then calculated as the reciprocal of the time to next state.

The probability of progression in each 3-month cycle was calculated as per the following formula:

$$p_{i \rightarrow i+1} = 1 - \exp \left(\frac{\text{rate of eGFR decline}}{4 * (M_i - M_{i+1})} \right)$$

Where rate of eGFR decline is the reciprocal of the time to next state, as above, $p_{i \rightarrow i+1}$ is the probability of progressing from CKD stage i to CKD stage $i + 1$ and M_i is the eGFR value at the midpoint of stage i . Since CKD stage 1 is defined as $\text{eGFR} \geq 90 \text{ mL/min/1.73m}^2$ and thus has no upper bound, the mean eGFR value of patients in CKD stage 1 at baseline in APPEAR-C3G was used as the midpoint instead ($116.9 \text{ mL/min/1.73m}^2$).

To further facilitate the EAG's understanding, please find a worked example for calculation of the probability of CKD stage 2 patients transitioning to CKD stage 3a with SoC in a 3-month cycle:

- CKD stage 2 is defined as $\text{eGFR} \geq 60$ to $< 90 \text{ mL/min/1.73m}^2$. The CKD stage 2 midpoint is calculated as $75 \text{ mL/min/1.73m}^2 (=60+(90-60)/2)$
- CKD stage 3a is defined as $\text{eGFR} \geq 45$ to $< 60 \text{ mL/min/1.73m}^2$. The CKD stage 3a midpoint is $52.5 \text{ mL/min/1.73m}^2 (=45+(60-45)/2)$
- The difference between CKD stage 2 and CKD stage 3a midpoints is $22.5 \text{ mL/min/1.73m}^2 (=75-52.5)$
- With an annual eGFR decline of $-7.224 \text{ mL/min/1.73m}^2$ in the SoC arm, it takes 3.11 years to progress from the CKD stage 2 midpoint to the CKD stage 3a midpoint ($=22.5/7.224$)

- e) This gives an annual rate of progression from CKD stage 2 to CKD stage 3a of 0.32 (=1/3.11)
- f) This results in a probability of 7.71% for progressing from CKD stage 2 to CKD stage 3a in a 3-month model cycle (=1-EXP(-0.32/4))

c) Please provide an updated economic model and scenario analysis:

- I. Using RaDaR data to inform treatment effectiveness of SoC.
- II. Apply the iptacopan treatment effect that was observed in the double-blind period (i.e. option 1 of CS Table 34) to SoC as modelled in I. to inform treatment effectiveness of iptacopan.

The scenario analysis has been conducted as requested by the EAG, with eGFR slope inputs shown in Table 15 and cost-effectiveness results shown in Table 16. From RaDaR data, an eGFR slope of $-4.0 \text{ mL/min/1.73 m}^2/\text{year}$ (all C3G patients, $n=139$) was available to inform disease progression in the SoC arm.¹² Application of an iptacopan treatment effect of $3.053 \text{ mL/min/1.73 m}^2/\text{year}$ (based on the 6-month double-blind period of APPEAR-C3G) to the RaDaR slope results in an iptacopan slope of $-0.947 \text{ mL/min/1.73 m}^2/\text{year}$.

When reviewing the eGFR slope inputs and resulting model outputs with regards to clinical plausibility, two UK clinicians consulted by Novartis during preparation of the clarification questions response expressed concerns regarding combining data from two different sources and differences in the included populations.⁸ While APPEAR-C3G enrolled patients with UPCR $\geq 1 \text{ g/g}$ (despite treatment with a maximally tolerated ACEi/ARB), the RaDaR eGFR slope was generated based on all C3G patients in the registry, including patients who had milder disease (UPCR $< 1 \text{ g/g}$). Given that high UPCR indicates an increased risk of rapid eGFR decline, clinicians highlighted that for the subgroup of patients reflecting the APPEAR-C3G inclusion criteria (UPCR $\geq 1 \text{ g/g}$), they would expect a steeper eGFR slope with SoC than informed by the RaDaR analysis in all C3G patients.⁸ As this represents an important limitation of the requested scenario analysis,⁸ results should be interpreted with caution.

Please note that based on clinical advice,⁸ this scenario analysis uses patient characteristics from RaDaR (as reflected in CS Table 33), in alignment with the source of the SoC eGFR slope.

Table 15: eGFR slope inputs for the economic model

Option	Population	Analysis	Annual eGFR slope, mL/min/1.73 m ² /year (95% CI)			Use in economic model
			SoC	Iptacopan	Iptacopan treatment effect	
1	APPEAR-C3G	- SoC: placebo arm data from 6-month double-blind period (N=36) - Iptacopan: iptacopan arm data from 6-month double-blind period (N=38)	-3.079 (-10.131, 3.973)	-0.025 (-6.929, 6.878)	3.053 (-6.815, 12.922)	Scenario analysis
2	APPEAR-C3G	- SoC: pre-iptacopan data, up to 2.5 years (N=74) - Iptacopan: on-iptacopan data, up to 2 years treatment duration^a (N=74)	-7.224 (-10.101, -4.348)	-0.289 (-3.884, 3.305)	6.935 (3.481, 10.390)	Base case
3	Pooled population: APPEAR-C3G and Phase 2 native kidney cohort (Cohort A)	- SoC: pre-iptacopan data, up to 2.5 years (N=90) - Iptacopan: on-iptacopan data, up to 4.7 years treatment duration^a (N=90)	-8.317 (-10.891, -5.744)	-0.701 (-3.765, 2.363)	7.616 (4.616, 10.616)	Scenario analysis
Additional scenario analyses requested by the EAG						
4	RaDaR and APPEAR-C3G	- SoC: RaDaR C3G population (N=139) - Iptacopan treatment effect from 6-month double-blind period (N=38)	-4.0 (-5.4, -2.6)	-0.947 <i>(calculated from SoC slope and iptacopan treatment effect)</i>	3.053 (-6.815, 12.922)	Scenario analysis: EAG request B7 c)
5	APPEAR-C3G	- SoC: pre-iptacopan data, up to 2.5 years (N=74) - Iptacopan treatment effect from 6-month double-blind period (N=38)	-7.224 (-10.101, -4.348)	-4.171 <i>(calculated from SoC slope and iptacopan treatment effect)</i>	3.053 (-6.815, 12.922)	Scenario analysis: EAG request B7 d)

Pre-iptacopan data includes historical values (up to 2 years prior to trial enrolment or since C3G diagnosis if less than 2 years), screening/run-in data and placebo arm data from the 6-month double-blind period of APPEAR-C3G. On-iptacopan data includes all data from initiation of iptacopan treatment, including data from patients originally randomised to the placebo arm of APPEAR-C3G after switching to open-label iptacopan at Day 180. ^aIncluding treatment in the open-label extension study.

Abbreviations: C3G, complement 3 glomerulopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; NR, not reported; SoC, standard of care.

Sources: Novartis Data on File. 2024 (APPEAR-C3G clinical study report; final analysis for adult data; Table 14.2-16.2.1);⁹ Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 1 Tables 2-1.2 and 2-1.1);¹⁰ Novartis Data on File. 2024 (RaDaR priority analysis interim enrichment report).¹²

d) Please provide an updated economic model and scenario analysis:

- I. Using the pre-iptacopan data (i.e. option 2 of CS Table 34), including up to 2.5 years of following (N=74) to inform treatment effectiveness of SoC.
- II. Apply the iptacopan treatment effect that was observed in the double-blind period (i.e. option 1 of CS Table 34) to SoC as modelled in I. to inform treatment effectiveness of iptacopan.

The scenario analysis has been conducted as requested by the EAG, with eGFR slope inputs shown in Table 15 and cost-effectiveness results shown in Table 16. Combining the SoC eGFR slope of $-7.224 \text{ mL/min/1.73 m}^2/\text{year}$ (pre-iptacopan, APPEAR-C3G population) with the iptacopan treatment effect of $3.053 \text{ mL/min/1.73 m}^2/\text{year}$ (based on the 6-month double-blind period of APPEAR-C3G) results in an iptacopan slope of $-4.171 \text{ mL/min/1.73 m}^2/\text{year}$.

Two UK clinicians consulted by Novartis during preparation of the clarification questions response cautioned against combining SoC and iptacopan eGFR slopes from different analyses.⁸ The clinicians flagged that a predicted iptacopan slope of $-4.171 \text{ mL/min/1.73 m}^2/\text{year}$ was inconsistent with the trial data, which suggested stabilisation of eGFR decline with iptacopan (e.g. on-iptacopan slope for APPEAR-C3G patients including extension study data: $-0.289 \text{ mL/min/1.73 m}^2/\text{year}$; see Table 15).⁸ They further highlighted that a predicted slope of $-4.171 \text{ mL/min/1.73 m}^2/\text{year}$ indicated steeper eGFR decline with iptacopan than with placebo based on the 6-month double-blind period ($-3.079 \text{ mL/min/1.73 m}^2/\text{year}$; see Table 15).⁸ In addition, it was noted that this would also result in modelling steeper eGFR decline with iptacopan than with SoC based on RaDaR data ($-4.0 \text{ mL/min/1.73 m}^2/\text{year}$; see Table 15).¹²

On that basis, clinicians considered the iptacopan eGFR slope used in this scenario analysis implausible and not supported by the available trial data,⁸ and results of this scenario analysis should be interpreted in that context.

Table 16: Scenario analysis results: Alternative eGFR slope inputs

Scenario	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	% change in ICER (versus revised base case)
Revised company base case (Analysis #2 in CEM: APPEAR-C3G (12 mo.) + Extension)	██████	16.88	£355,162	15.13	██████	1.74	██████	N/A
RaDaR data for SoC and iptacopan treatment effect from APPEAR-C3G (6-month double-blind period) (Analysis #4 in CEM)	██████	16.86	£288,267	15.70	██████	1.16	██████	██████
Pre-iptacopan slope for SoC and iptacopan treatment effect from APPEAR-C3G (6-month double-blind period) (Analysis #5 in CEM)	██████	15.78	£355,162	15.13	██████	0.64	██████	██████

Result presented are using RaDaR data to inform treatment effectiveness of SoC and applying the iptacopan treatment effect that was observed in the double-blind period (i.e. option 1 of CS Table 34) to SoC to inform treatment effectiveness of iptacopan and using the pre-iptacopan data (i.e. option 2 of CS Table 34) including up to 2.5 years of following (N=74) to inform treatment effectiveness of SoC, and applying the iptacopan treatment effect that was observed in the double-blind period (i.e. option 1 of CS Table 34) to SoC to inform treatment effectiveness of iptacopan

Abbreviations: CEM: cost-effectiveness model; EAG: external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years SoC: standard of care.

- e) In the CS, it was stated that “While the rate of eGFR decline may vary over the course of disease, the sample size of the iptacopan trials in C3G did not permit estimation of CKD stage-dependent eGFR decline rates. As such, a simplifying assumption that speed of progression is independent of CKD stage and constant over the course of disease was applied”. Please elaborate on the clinical plausibility of this assumption and the implications on the modelled outcomes (i.e. health state costs, particularly for dialysis and transplants, and health state utilities).

The clinical plausibility of the assumed constant speed of eGFR progression was discussed with clinical experts as part of a UK clinical advisory board. Clinicians noted that while eGFR slope would be expected to fluctuate, the overall path of disease in C3G is a progressive decline and therefore a linear slope was a reasonable simplification. Advisors also noted that in C3G, eGFR decline does not tend to get steeper as patients get closer to kidney failure, unlike other kidney diseases.⁴ Two UK clinicians consulted during preparation of the clarification questions response reconfirmed that an assumption of a linear slope was reasonable and in line with how eGFR data was generally considered in research in nephrology.⁸

- f) Despite the sample size issue (combining CKD stages, i.e. stages 3A and B and stage 4 and 5, could be considered), please provide an updated economic model and scenario analyses exploring
- I. CKD stage-dependent eGFR decline rates from the iptacopan trials in C3G. If not deemed feasible based on the data currently available, please use other literature or evidence (e.g. external data and/or expert opinion).

Table 17 below shows an analysis of eGFR slope stratified by baseline CKD stage 1 (eGFR ≥ 90 mL/min/1.73 m²) and CKD stages 2–4 (eGFR < 90 mL/min/1.73 m²). Patients in APPEAR-C3G (including extension study data) with baseline eGFR ≥ 90 mL/min/1.73 m² had a similar on-iptacopan slope per year (–0.880) as patients with baseline eGFR < 90 mL/min/1.73 m² (–0.298). Please note that an analysis breaking down the data into further CKD stages was not considered feasible due to very small patient numbers in higher CKD stages (also see response to question B7 g) below).

Table 17: Model estimated eGFR (mL/min/1.73m²) slopes per year stratified by baseline eGFR – APPEAR-C3G population including extension study data (FAS)

Baseline eGFR	Intercept	Pre-iptacopan eGFR slope per year (95% CI)	On-iptacopan eGFR slope per year (95% CI)	Slope change per year (95% CI)	p-value
≥90 mL/min/1.73 m ² (N=43)	117.545 (113.558, 121.533)	-2.023 (-4.960, 0.915)	-0.880 (-4.355, 2.595)	1.142 (-2.649, 4.934)	0.5465
<90 mL/min/1.73 m ² (N=31)	62.904 (54.580, 71.229)	-14.406 (-19.681, -9.132)	-0.298 (-6.875, 6.279)	14.109 (8.350, 19.867)	<.0001

eGFR slopes per year were analysed using a linear mixed effects model including time (analysis day before or after change point (day 1 of iptacopan treatment)) as a continuous covariate, participant-level intercept and slope (time) as random effects.

Abbreviations: CI, confidence interval; eGFR: estimated glomerular filtration rate; FAS, full analysis set.

Source: Novartis Data on File. 2024 (Summary of Clinical Efficacy in C3 Glomerulopathy; Appendix 1; Table 2-1.2.5 and Table 2-1.2.6).⁵²

eGFR slope data from C3G patients in RaDaR by eGFR at baseline is presented in Table 18 below.

Table 18: Model estimated eGFR (mL/min/1.73m²) slopes per year stratified by baseline eGFR – RaDaR C3G cohort

Baseline eGFR	N	Mean (SD) length of follow-up (years)	eGFR slope per year (95% CI)
≥60 mL/min/1.73 m ²	53	9.4 (5.6)	-5.1 (-7.6, -2.8)
45-60 mL/min/1.73 m ²	10	6.7 (5.1)	-5.2 (-10.7, 0.3)
30-45 mL/min/1.73 m ²	12	6.2 (3.9)	-0.5 (-8.6, 7.6)
<30 mL/min/1.73 m ²	16	2.9 (3.3)	-3.3 (-6.2, -0.2)

Linear mixed models were used to estimate annualised eGFR slopes. Patients were required to have at least 4 eGFR values to be included in the analysis, and a mixed model was used to account for the multiple values per patient. During the modelling, eGFR slope was assumed to be linear.

Abbreviations: CI, confidence interval; eGFR: estimated glomerular filtration rate; SD, standard deviation.

Source: Novartis Data on File. 2024 (C3G RaDaR Priority Analysis, Interim Enrichment Report).¹²

Both the analysis of iptacopan trial data and the RaDaR analysis have the limitation that eGFR decline rates are stratified by a patient's CKD stage at baseline, rather than providing the rate of decline while in a specific CKD stage (as would be required as a model input). Such an analysis was deemed infeasible for iptacopan trial data due to sample size and the small number of patients in higher CKD stages (see also response to question B7 g) below). With regards to the data available from RaDaR, clinicians did not consider it plausible that eGFR slope would be less steep for patients with baseline CKD stage 3b (eGFR 30–45 mL/min/1.73 m²) compared to patients diagnosed in other CKD stages, and highlighted the small sample size of the individual CKD stage subgroups.⁸ Since the available data were not considered suitable for use in the economic model, and clinicians had further confirmed that an assumption of linear eGFR decline over the disease course was reasonable (see response to question B7 e) above), no scenario analysis was implemented in the model.

- II. Time-dependent eGFR decline rates from the iptacopan trials in C3G. If not deemed feasible based on the data currently available, please use other literature or evidence (e.g. external data and/or expert opinion).

eGFR decline rates for the double-blind and open-label periods of APPEAR-C3G are presented in the response to question A7 (Table 5). However, as highlighted, UK clinicians advised that a time frame of 6 months may be too short to robustly estimate changes in eGFR,⁴ therefore, these estimates by treatment period (each based on 6 months of data) should be interpreted with caution, with eGFR slope analyses based on longer follow-up considered more robust and meaningful by clinical advisors.^{4, 8} Therefore, no scenario analysis was implemented in the model.

- g) Generating transition probabilities from observed transitions between CKD stages was not considered due to the small sample size and low patient numbers in more advanced CKD stages at baseline. Despite the small sample size and low patient numbers, please provide an updated economic model and explore this approach in a scenario analysis.

Based on the EAG's request, generation of transition probabilities based on observed transitions between CKD stages in APPEAR-C3G has been attempted, with outputs provided in the following tables. Table 19 and Table 20 present the transition probabilities per 3-month model cycle based on observed CKD stage transitions in APPEAR-C3G for the SoC arm (based on placebo data) and the iptacopan arm, respectively. Due to placebo arm patients switching to iptacopan after the completion of the 6-month double-blind period, SoC transitions could only be informed by 6 months of data (two cycles). Data from patients allocated to the placebo arm following switch to iptacopan at the start of the open-label period were combined with the iptacopan arm data for months 0 to 3 and months 3 to 6, in order to use all available on-iptacopan data.

As visible in the tables below, the patient counts are very low, especially in more advanced CKD stages, resulting in non-meaningful transition probabilities. In the SoC arm (Table 19), based on transition probabilities generated from observed transitions in 36 patients over 6 months, patients in CKD stage 1 or 2 at baseline never progress beyond CKD stage 2, while patients in CKD stage 3a at baseline remain in 3a indefinitely and patients in CKD stage 3b at baseline remain in 3b indefinitely. If used in the economic model, patients on SoC would therefore never progress to kidney failure, which is implausible and inconsistent with available real-world data from multiple sources indicating a median time to kidney failure of 10 years with current SoC. Data for iptacopan (Table 20) is available from APPEAR-C3G for overall 4 model cycles, with the full trial population (N=74) contributing data for transitions for the first 6 months (due to the placebo arm cross-over); however, transitions from CKD stage 3a or higher are still only informed by single-digit patient numbers and thus not considered robust. Therefore, this approach was not considered suitable to provide valid transition probabilities for economic modelling, due to sample size limitations inherent to evidence generation in ultra-rare diseases, and thus not implemented as a scenario analysis.

Previous appraisals in CKD which utilised the above approach benefitted from substantially larger sample sizes in their respective clinical trials; for example, the pivotal trial for finerenone in adults with CKD and type 2 diabetes included 5,674 patients (TA877)⁵³ and the pivotal trial for

dapagliflozin in adults with CKD included 4,304 patients (TA775),²⁹ compared to 74 patients in the APPEAR-C3G trial informing this submission.

However, it should be highlighted that even though the approach to generating transition probabilities in this submission differs, it equally relies on observed eGFR data. While deriving transition probabilities based on observed CKD stage transitions utilises eGFR as categorical data, eGFR slope – as used in this submission – utilises eGFR as continuous data. Therefore, the selected eGFR slope approach incorporates all observed changes in eGFR, rather than only observed changes in eGFR which resulted in a patient crossing the threshold to another CKD stage.

Overall, the selected eGFR slope approach can be considered to use data more efficiently, which is especially important with a small sample size, as in this submission.

Table 19: SoC transition probabilities based on observed CKD stage transitions in APPEAR-C3G (placebo)

	Patient counts						Transition probabilities					
	Month 0 to 3						Month 0 to 3					
To From	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5
CKD stage 1	█	█					█	█	█	█	█	█
CKD stage 2	█	█					█	█	█	█	█	█
CKD stage 3a			█				█	█	█	█	█	█
CKD stage 3b				█			█	█	█	█	█	█
CKD stage 4							N/A	N/A	N/A	N/A	N/A	N/A
CKD stage 5							N/A	N/A	N/A	N/A	N/A	N/A
	Month 3 to 6						Month 3 to 6					
To From	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5
CKD stage 1	█	█					█	█	█	█	█	█
CKD stage 2	█	█					█	█	█	█	█	█
CKD stage 3a			█				█	█	█	█	█	█
CKD stage 3b				█			█	█	█	█	█	█
CKD stage 4							N/A	N/A	N/A	N/A	N/A	N/A
CKD stage 5							N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: CKD, chronic kidney disease; N/A, not applicable; SoC, standard of care.

Source: Novartis Data on File. 2025 (Clarification questions supplementary analyses – Section B7).¹¹

Table 20: Iptacopan transition probabilities based on observed CKD stage transitions in APPEAR-C3G

	Patient counts							Transition probabilities*					
	Month 0 to 3							Month 0 to 3					
To From	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	Missing	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5
CKD stage 1													
CKD stage 2													
CKD stage 3a													
CKD stage 3b													
CKD stage 4													
CKD stage 5								N/A	N/A	N/A	N/A	N/A	N/A
Missing													
	Month 3 to 6							Month 3 to 6					
To From	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	Missing	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5
CKD stage 1													
CKD stage 2													
CKD stage 3a													
CKD stage 3b													
CKD stage 4													
CKD stage 5								N/A	N/A	N/A	N/A	N/A	N/A
Missing													

		Month 6 to 9						Month 6 to 9						
To	From	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	Missing	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5
CKD stage 1		█	█						██	██	██	██	██	██
CKD stage 2		█	█		█				██	██	██	██	██	██
CKD stage 3a				█					██	██	██	██	██	██
CKD stage 3b					█	█			██	██	██	██	██	██
CKD stage 4							█		██	██	██	██	██	██
CKD stage 5									N/A	N/A	N/A	N/A	N/A	N/A
		Month 9 to 12							Month 9 to 12					
To	From	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	Missing	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5
CKD stage 1		█	█						██	██	██	██	██	██
CKD stage 2		█	█						██	██	██	██	██	██
CKD stage 3a				█					██	██	██	██	██	██
CKD stage 3b				█	█	█			██	██	██	██	██	██
CKD stage 4							█		██	██	██	██	██	██
CKD stage 5							█		██	██	██	██	██	██

Footnote: *Patients with missing CKD stage data at either the 'from' or 'to' timepoint were excluded from the analysis for that time period when calculating transition probabilities.

Abbreviations: CKD, chronic kidney disease; N/A, not applicable; SoC, standard of care.

Source: Novartis Data on File. 2025 (Clarification questions supplementary analyses – Section B7).¹¹

- h) Please validate the use of eGFR slopes for estimating CKD transitions against real-world data in different populations.

As we understood from the EAG during the clarification call, this request relates to a comparison of outcomes when using eGFR slope versus using transition probabilities derived from observed CKD stage changes, based on an assessment of economic evaluations conducted e.g. in other chronic kidney diseases. Table 31 of the CS summarises how CKD progression was modelled in previous NICE appraisals, but no appraisals could be identified which conducted and compared both of these approaches. Therefore, it was not possible to perform any validation of the selected eGFR slope approach based on previous appraisals.

B 8. Priority question. The iptacopan discontinuation rate (0.063 per year, with a per cycle probability of discontinuation of 1.57%.) among patients who have not reached kidney failure was based on all-cause treatment discontinuation of iptacopan in the pooled APPEAR-C3G, Phase 2 and extension studies (broad safety set).

- a) Please comment on the (clinical) plausibility of the iptacopan discontinuation rate in the company's base-case.

The iptacopan discontinuation rate was based on all-cause treatment discontinuation data from the broad safety set, including APPEAR-C3G, the Phase 2 study and the open-label extension study, with overall 189.8 patient-years of exposure.¹⁷ One discontinuation due to death (among overall 13 discontinuations) was excluded from the calculation of the discontinuation rate for the economic model, since mortality was modelled separately. Given that the discontinuation rate was derived from all available iptacopan trial evidence in C3G, it represents the best source of data. Clinical experts considered the discontinuation rate plausible and supported its use for the economic model base case.⁸

- b) Please justify and provide evidence for the assumption of modelling the iptacopan discontinuation rate to be constant over time.

Discontinuations were observed throughout the clinical trials, with no marked accumulation of either early or late discontinuations. Therefore, a constant discontinuation rate was considered a reasonable assumption for the company base case. However, time-varied discontinuation rates are explored in the response to question B8 e).

- c) Please provide an updated economic model and scenario analyses (informed by external data, expert inputs and/or other TAs in chronic kidney disease):

I. exploring alternative discontinuation rates

In line with the above response to clarification question B8 a), the trial-derived discontinuation rate is considered clinically plausible by the consulted experts⁸ and represents the best available evidence for discontinuations of iptacopan in C3G to date, and thus has been retained as the base case input.

Treatment discontinuation rates from other CKD TAs are not considered relevant for this appraisal, given the differences both in interventions and conditions versus the current decision problem.

The rate of discontinuation, found in cell C49 of the 'Clinical data' tab, is varied within the DSA and was shown not to be a key model driver (see Figure 18).

II. exploring time-varying discontinuation rates

Time-varying discontinuation rates are explored within the economic model through time to treatment discontinuation (TTD) analysis in response to questions B8 d) and B8 e).

- d) Please provide time to treatment discontinuation (TTD) analyses for both the pooled data and for the APPEAR-C3G trial only (including Kaplan-Meier analyses, parametric survival analyses as well as exploring the (cumulative) hazard over time and other diagnostic plots consistent with NICE DSU TSD 14).

TTD analysis was conducted for both the pooled (broad safety set) and APPEAR-C3G-only populations. Same as for the calculation of the constant discontinuation rate (as used in the company base case), one discontinuation due to death was excluded from the survival analysis, and censored. The Kaplan-Meier plot with parametric survival extrapolations for the pooled population, as the most comprehensive source of evidence, is presented below in Figure 3. The corresponding plot for the APPEAR-C3G population, as well as cumulative hazard plots over time for both populations can be found within the "B8 - Parametric survival analysis" section of the reference pack document titled 'Clarification questions supplementary analyses'.¹¹

Figure 3: Parametric survival analysis for iptacopan discontinuations, pooled (broad safety set) population



Source: Novartis Data on File (Clarification questions supplementary analyses – Section B8).¹¹

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

- e) Please provide an updated economic model and scenario analyses informing treatment discontinuation of iptacopan and SoC in the economic model based on the parametric survival analyses in c) and provide justification for the selected curves.

Parametric survival analysis for iptacopan discontinuations has been added to the model and can be found in rows 52 onwards of the 'Settings' tab, with trial data sources and parametric survival curves for selection in cells C39 and C40, respectively. Standard extrapolations, in line with NICE DSU TSD 14, were explored (exponential, Weibull, lognormal, log logistic, Gompertz and generalised gamma).⁵⁴

Table 21 shows the statistical fits for each extrapolation for both the pooled and APPEAR-C3G populations. The pooled population (broad safety set) is considered the most appropriate data source, since it contains all iptacopan C3G data. APPEAR-C3G-only data is presented for completeness only.

As visible from Table 21, for the pooled population, an exponential curve shows the best statistical fit for BIC with the third best statistical fit for AIC. The log-normal curve has the best fit for AIC and is ranked second for BIC. Clinical experts considered the exponential extrapolation most plausible and also suggested that in clinical practice, outside a double-blind clinical trial setting, some discontinuations may occur early if no response is seen,⁸ which was found to be reflected best by the exponential curve. Weibull or Gompertz extrapolations were not considered plausible by the experts.⁸

Table 21: Statistical fit ranking (AIC and BIC) of parametric survival extrapolations

Scenario	Pooled trial data (broad safety set)		APPEAR-C3G	
	AIC	BIC	AIC	BIC
Exponential	3	1	1	1
Log-normal	1	2	2	2
Log-logistic	2	3	3	3
Weibull	4	4	4	4
Gompertz	5	5	5	5
Generalised gamma	6	6	6	6

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

Table 22 shows scenario analysis results with the best-fitting TTD extrapolations, for both the pooled and APPEAR-C3G trial-only populations, for the two top fitting curves for each of AIC and BIC (exponential and log normal). As noted, APPEAR-C3G-only data disregards discontinuations occurring in the broader safety set, and the pooled data are considered the more appropriate source of information. There was limited impact on the ICER regardless of the selected parametric curve across both populations (■■■■ to ■■■■ change in ICER versus the revised base case across all scenarios)

Table 22: Scenario analysis results: Iptacopan time to treatment discontinuation (TTD) using parametric survival extrapolations

Extrapolation	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			% change in ICER versus revised base case
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	
Revised company base case								
Constant discontinuation, 1.57% probability per cycle	████████	16.88	£355,162	15.13	████████	1.74	████████	N/A
Scenario analyses with TTD derived from pooled population (broad safety set)								
Exponential	████████	16.88	£355,162	15.13	████████	1.75	████████	████████
Log-normal	████████	16.81	£355,162	15.13	████████	1.67	████████	████████
Scenario analyses with TTD derived from APPEAR-C3G population only								
Exponential	████████	17.09	£355,162	15.13	████████	1.95	████████	████████
Log-normal	████████	16.82	£355,162	15.13	████████	1.69	████████	████████

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; SOC: standard of care; TTD: time to treatment discontinuation.

B 9. Priority question. In the company's base-case, a constant iptacopan treatment effect was assumed over the model time horizon while patients remained on treatment.

- a) Please justify the assumption of no treatment waning, i.e. that there is a constant lifetime iptacopan treatment effect.

In C3G, overactivation of the complement alternative pathway leads to deposition of C3 within the glomeruli of the kidneys, triggering inflammation and glomerular injury.⁷ Iptacopan is a proximal complement inhibitor that specifically binds Factor B. This selectively blocks alternative pathway overactivation by inhibiting alternative pathway-related C3 convertase activity, leading to decreased cleavage of C3 and reduced C3 deposition in the kidney.²

The ability of iptacopan to inhibit the alternative pathway was assessed with APPEAR-C3G through the examination of circulating biomarker levels, including serum C3 and alternative pathway activity, presented on pages 65 and 66 of the CS. Iptacopan demonstrated rapid and sustained effects on multiple biomarkers for complement alternative pathway dysregulation.⁹ This confirms the disease-modifying effect of iptacopan which translated into effects on proteinuria and eGFR, which were sustained throughout APPEAR-C3G and the open-label extension study.^{9, 10}

In the model validation call conducted prior to the CS, the clinical advisor explained that the pharmacological effect of iptacopan will not change over time and therefore, the treatment effect is not expected to wane.⁵ This was again confirmed in a call with two clinicians during preparation of the clarification questions response.⁸ The clinicians explained that the pathophysiology of C3G (complement alternative pathway overactivation leading to C3 deposition in the glomeruli) is well understood and does not change over time. Similarly, the mechanism of action of iptacopan (blocking complement alternative pathway overactivation and reducing C3 deposition in the glomeruli) and how it targets C3G is also well understood, therefore, the experts concluded that there was no plausible scientific rationale to expect the pharmacological effect of iptacopan to wane over time.⁸

Treatment effect waning was not considered to apply in the appraisal of iptacopan in paroxysmal nocturnal haemoglobinuria (PNH; TA1000).¹⁹ This was consistent with previous NICE appraisals of other complement inhibitors in PNH (TA698 and TA778),^{55, 56} as well as in atypical haemolytic uraemic syndrome (aHUS).^{57, 58} Complement inhibitors in aHUS were also cited as an example by the consulted clinicians, where they had not observed evidence of treatment effect waning in their extensive personal clinical experience.⁸

Clinicians further highlighted the strength of the pooled iptacopan C3G trial analyses, with up to 4.7 years of data available from Phase 2 trial patients who continued iptacopan treatment in the open-label extension study, suggesting stabilisation of eGFR;⁸ these data are summarised in Section 2.8 of the CS and utilised in a scenario analysis in the economic model (see CS Table 34, option 3; scenario results reported in CS Table 60). They further emphasised that disease progression in C3G patients treated with iptacopan does not necessarily equate to treatment effect waning.⁸ While the trial data suggest stabilisation of eGFR with iptacopan, this represents an average and outcomes of individual patients will vary. For example, in patients who already have established fibrosis when starting iptacopan, eGFR is expected to decline since irreversible

kidney damage and chronic kidney disease are already present, but iptacopan is still expected to lead to better outcomes for these patients compared to current SoC.⁸

Based on their understanding of the disease and the mode of action of iptacopan, available trial data, and their clinical experience with iptacopan and other complement inhibitors, the consulted clinicians considered it inappropriate to incorporate non-evidence-based waning assumptions into the economic modelling.⁸

b) Please provide time-to-event data on CKD progression (i.e., CKD progression-free survival) for iptacopan + SoC versus SoC alone. Specifically, please analyse time-to-event data separately for progression to CKD stages 2, 3, 4, and 5, as well as for time to dialysis, death, or transplant:

- Handling of patients with prior events: include all APPEAR-C3G patients in these analyses. If patients already had the event before the analysis started (e.g., patients in CKD stage 2 for the time-to-CKD-stage-2 analysis), please include these patients as having the event at day 1.
- Tabulated data: provide time-to-event data at different time points for CKD stages 2, 3, 4, and 5 for both treatment arms.
- Kaplan-Meier plots: present Kaplan-Meier survival curves for CKD progression-free survival, stratified by treatment arm. Include the number of patients at risk at multiple time points (e.g. every 3 months).
- Hazard plots: provide hazard plots over time.
- Cumulative hazard plots: provide cumulative hazard plots over time.
- Cox proportional hazards analysis: perform a Cox regression analysis and include Schoenfeld residuals plots to assess the proportional hazards assumption.

As outlined in the response to question B7 g), a limited number of CKD stage transitions were observed during APPEAR-C3G; participants mostly remained in their original CKD stage throughout follow up. In addition, the number of participants in later CKD stages at baseline was very small. Since the analysis of CKD stage transition probabilities conducted for question B7 g) did not yield meaningful results, it was considered that the same limitations would apply to time-to-event analyses on the same set of data. Therefore, the requested analyses were not considered feasible.

- c) Please justify, based on the analyses above, assuming a constant treatment effect of iptacopan over the model time horizon.

Please refer to the response to question B9 a) above.

- d) Please provide an updated economic model and scenario analyses exploring waning of the iptacopan treatment effect (at different time points).

Given the strong clinical opinion against treatment waning scenarios outlined in the response to question B9 a), this has not been provided.

Adverse events

B 10. In the CS, data from the pooled safety set informed serious AEs (SAEs) suspected to be related to iptacopan which were included in the analyses.

- a) Please explain the rationale and thresholds (severity grade 3 or 4) of including SAEs “suspected to be related to iptacopan”, with severity grades likewise requested by the health economics advisor from the CS “Clinical and Model Validation for Iptacopan in C3G”.

Severity grade ≥ 3 corresponds to an AE classification as “severe” in the iptacopan C3G clinical trial reporting. In the double-blind, placebo-controlled period of APPEAR-C3G, 2 severe AEs occurred in the iptacopan arm and one severe AE in the placebo arm, with none of the reported severe AEs occurring in more than one patient.⁹

To ensure the impact of AEs associated with iptacopan which would be likely to affect QALYs and costs was captured in the model, *serious AEs (SAEs)* suspected to be related to iptacopan were included. SAEs were defined in the trial protocol as any AEs that are fatal, life-threatening, result in persistent or significant disability/incapacity, constitute a congenital anomaly/birth defect, require inpatient hospitalisation (or prolongation of existing hospitalisation), or are medically significant in the sense that they jeopardise the participant or may require medical intervention to prevent one of the outcomes listed above.⁵⁹ On that basis, SAEs were selected because they were expected to have meaningful disutility and cost implications; this approach aligns with how AEs were modelled in the NICE appraisal of iptacopan for its first indication, PNH (TA1000).¹⁹

The rationale for only modelling SAEs *suspected to be related to iptacopan* followed the decision to use data from the broad safety set, rather than the controlled safety set (see response to question B10 b) below). In controlled data with a sufficiently large sample size, AEs that are not associated with the intervention or comparator but occur by chance would be expected to occur at equal rates in both arms of the trial, with effects of these AEs on QALYs and costs ultimately cancelling out in the economic model. Since the broad safety set only reports on iptacopan AEs and does not contain a control arm, it only provided data for modelling AEs for iptacopan (with no AEs modelled for the SoC comparator arm). Use of *all* SAEs from the broad safety set in the model would have attributed also AEs that occurred by chance to iptacopan. The list of SAEs which occurred in the broad safety set was reviewed with two UK clinicians, who considered it unjustified to assign events which were classified as unrelated to iptacopan (such as [cocaine]

overdose, appendicitis or tendon rupture) to iptacopan in the economic model.⁸ Given the available evidence, the decision to model only SAEs suspected to be related to iptacopan – while not modelling any AEs for the comparator arm – was supported by clinicians and is thus considered appropriate.⁸

A new scenario analysis explores the impact of modelling *severe* AEs (i.e. grade ≥ 3) suspected to be related to iptacopan; please see below in the response to question B10 d).

- b) Please explain why data from the broad safety set, having pooled trial populations was used instead of the controlled safety set.

The controlled safety set provides only six months of data as the duration of the double-blind, placebo-controlled period of APPEAR-C3G was limited to six months.⁹ On the other hand, the broad safety set includes all available iptacopan safety data from all iptacopan trials in C3G, with overall 189.8 patient-years of exposure.¹⁷

Using the controlled safety set would have excluded all iptacopan AEs which occurred after Month 6 of APPEAR-C3G, and all AEs which occurred in the Phase 2 study and the open-label extension study, from the analysis. Therefore, using the broad safety set as the more comprehensive set of data with substantially longer follow-up (up to 4.7 years iptacopan treatment duration) is a more conservative approach to fully capture the safety profile of iptacopan in the economic model.

- c) Please explain the simplifying approach of standardising all SAEs to pneumonia/sepsis (CS, Clinical and Model Validation for Iptacopan in C3G).

As noted on page 107 of the CS and presented in Table 23 (CS Table 38), almost all SAEs suspected to be related to iptacopan were infections with encapsulated bacteria (an AE of special interest for iptacopan) leading to pneumonia or consequences thereof such as sepsis.¹⁷ Therefore pneumonia/sepsis was considered accordingly in the economic analysis for AE disutilities and costs, calculating a weighted average across all severity scores of relevant NHS reference cost categories. While acknowledged as a simplification, it is expected that this approach appropriately captures AE disutilities and costs associated with iptacopan treatment. In addition, sensitivity analysis (DSA and scenario analysis) presented in the CS demonstrated very limited impact of AEs on cost-effectiveness results (see CS Section 3.10).

Table 23. SAEs suspected to be related to iptacopan treatment (broad safety set; N=101)

Patients	Day of onset	SAE suspected to be related to iptacopan
Patient 1	████	Blood culture positive (for streptococcus pneumoniae)
Patient 1 ^a	████	Pneumonia pneumococcal
	████	Pneumococcal sepsis
	████	Streptococcal bacteraemia (evolved to septic shock)
Patient 2	████	Pneumonia pneumococcal
	████	Septic shock
	████	Acute respiratory distress syndrome
Patient 3	████	Norovirus infection
Patient 4	████	Pneumocystis jirovecii pneumonia

^aSubsequent SAE episode

Abbreviations: SAE, serious adverse event.

Source: Novartis Data on File. 2024 (Summary of Clinical Safety in C3 Glomerulopathy, Table 2-5).¹⁷

d) Please provide an updated economic model and scenario analyses for both the controlled and broad safety set separately including the following alternatives each, while refraining from the simplifying assumption detailed in c).

- I. All SAEs irrespective of suspected relationship with iptacopan and grade
- II. All grade ≥ 3 AE (i.e. incidence $>0\%$)
- III. All grade ≥ 3 AE with an incidence of $\geq 5\%$

Table 24 presents the adverse event inputs used in the scenario analyses requested by the EAG. As summarised in the response to question B10 a), clinicians did not consider it reasonable to include AEs in the model which did not have a suspected relationship with iptacopan treatment,⁸ i.e. scenarios I. to III. as presented below. An additional scenario analysis has been added to the table by Novartis, considering causality of severe AEs (grade ≥ 3), in case there is overall a preference for capturing severe AEs rather than SAEs as utilised in the company base case.

In the controlled safety set, the total exposure was 18.3 patient-years (PYs) for iptacopan and 17.8 PYs for placebo.¹⁷ In the broad safety set, there were 189.8 PYs of exposure for iptacopan.¹⁷ Table 25 presents the requested scenario analysis results. The scenario analyses have a minimal impact, changing the ICER by -████ to +████ compared to the base case.

Table 24: Summary of AEs used in scenario analyses¹⁷

Scenario	Controlled safety set		Broad safety set
	Iptacopan 200 mg b.i.d. (N=38; 18.3 PYs)	Placebo (N=36; 17.8 PYs)	Iptacopan 200 mg b.i.d. (N=101; 189.8 PYs)
Scenario I: All SAEs irrespective of suspected relationship with iptacopan and grade	3	2	36
Scenario II: All grade ≥ 3 AEs (i.e. incidence $>0\%$)	2	1	17
Scenario III: All grade ≥ 3 AEs with an incidence of $\geq 5\%$	0	0	0
Additional scenario: All grade ≥ 3 AEs suspected to be related to iptacopan	1	N/A	5

Abbreviations: AE, adverse event; b.i.d., twice daily; n/a, not applicable; PY, patient years; SAE, serious adverse event.

Sources: Novartis Data on File. 2024. APPEAR-C3G Summary of Clinical Safety in C3 glomerulopathy, Table 2-1;¹⁷ Novartis Data on File. 2024. APPEAR-C3G Summary of Clinical Safety in C3 glomerulopathy Appendix 1, Listing 1.4-1¹⁷

Table 25: Scenario analysis results: Alternative AE incidence inputs

Scenario	Safety set	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			% change in ICER (versus revised company base case)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	
Revised company base case (SAEs suspected to be related to iptacopan)	Broad	██████	16.88	£355,162	15.13	██████	1.74	██████	N/A
Scenario analysis I: All SAEs irrespective of suspected relationship with iptacopan and grade	Controlled	██████	16.83	£363,479	15.09	██████	1.74	██████	██████
	Broad	██████	16.86	£355,162	15.13	██████	1.72	██████	██████
Scenario analysis II: All grade ≥3 AE (i.e. incidence >0%)	Controlled	██████	16.85	£359,350	15.11	██████	1.74	██████	██████
	Broad	██████	16.87	£355,162	15.13	██████	1.73	██████	██████
Scenario analysis III: All grade ≥3 AE with an incidence of ≥5%	Controlled	██████	16.88	£355,162	15.13	██████	1.74	██████	██████
	Broad	██████	16.88	£355,162	15.13	██████	1.74	██████	██████
Additional scenario analysis: All grade ≥3 AEs suspected to be related to iptacopan	Controlled	██████	16.87	£355,162	15.13	██████	1.74	██████	██████
	Broad	██████	16.88	£355,162	15.13	██████	1.74	██████	██████

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; SAE, serious adverse event; QALY, quality adjusted life year.

Health-related quality of life

B 11. Priority question. EQ-5D-5L data in the APPEAR-C3G study were mapped to EQ-5D-3L and health state utility values were estimated using a mixed effects linear model with repeated measures.

- a) Please argue why a mixed effects linear model with repeated measures is appropriate in this context.

When analysing longitudinal data, where there are repeated measures for each subject, observations of EQ-5D within each subject will be correlated, as a patient with a higher EQ-5D score at one time point is likely to have a higher EQ-5D score at later time points. This correlation violates the independence assumption of traditional fixed-effects models. Mixed effects models account for this correlation using random effects that quantify variation among subjects and serve to describe cluster-specific trends over time.^{60, 61}

For deriving utility values from EQ-5D data collected across multiple time points in APPEAR-C3G, a model allowing for a random intercept for each subject was used to account for intra-subject correlations. Mixed effects models have been widely used to analyse utility data for HTA submissions, including in the previous NICE appraisal of iptacopan for paroxysmal nocturnal haemoglobinuria (PNH; TA1000).¹⁹

- b) Please clarify to which extent repeated measurements were captured in the model, as CS Table 41 does not report a time variable.

The mixed effects model was used to account for repeated measurements for each subject, via the inclusion of subject-level random effects. A time variable was not included in the model. Table 26 presents the outputs of a model that accounts for time-effects by including fixed-effects covariates for each visit compared to baseline. The impact of including time-effects on other covariates is minimal.

Table 26: Analysis of EQ-5D data including time effects

	Coefficient	S.E.	LCI	UCI
CKD stage 3 (vs 1/2)				
CKD stage 4 (vs 1/2)				
Baseline EQ-5D centred on the mean				
Age				
Sex				
Day 14				
Day 30				
Day 90				
Day 180				
Day 210				
Day 270				
Day 360				
Constant				

Abbreviations: CKD, chronic kidney disease; LCI, lower confidence interval; S.E., standard error; UCI, upper confidence interval

- c) Please provide an overview of the number of HRQoL observations per time point of the data, the number and pattern of missingness, and how missing data were handled.

EQ-5D-5L data were collected in APPEAR-C3G at baseline, Day 14, 30, 90, 180, 210, 270, and 360. Table 27 presents a summary of the data at each time point. Missing data was minimal, with a maximum of 9% of study participants missing data at any timepoint. Data were assumed to be missing at random.

Table 27: Pattern of missing EQ-5D data in APPEAR-C3G

Time point	Population size (N)	Missing (N)	Missing (%)	Completed (N)	Completed (%)
Baseline	74	7	9%	67	91%
Day 14	74	7	9%	67	91%
Day 30	74	5	7%	69	93%
Day 90	74	6	8%	68	92%
Day 180	74	1	1%	73	99%
Day 210	74	1	1%	73	99%
Day 270	74	5	7%	69	93%
Day 360	74	2	3%	72	97%

- d) Please provide a list of all covariates that were considered from APPEAR-C3G for this regression model.

Covariates included in the regression model were CKD stage (as factor variables compared to CKD stage 1/2), age, sex and baseline EQ-5D (centred on the mean). Covariates were retained regardless of significance, as they are known to be predictors of HRQoL.

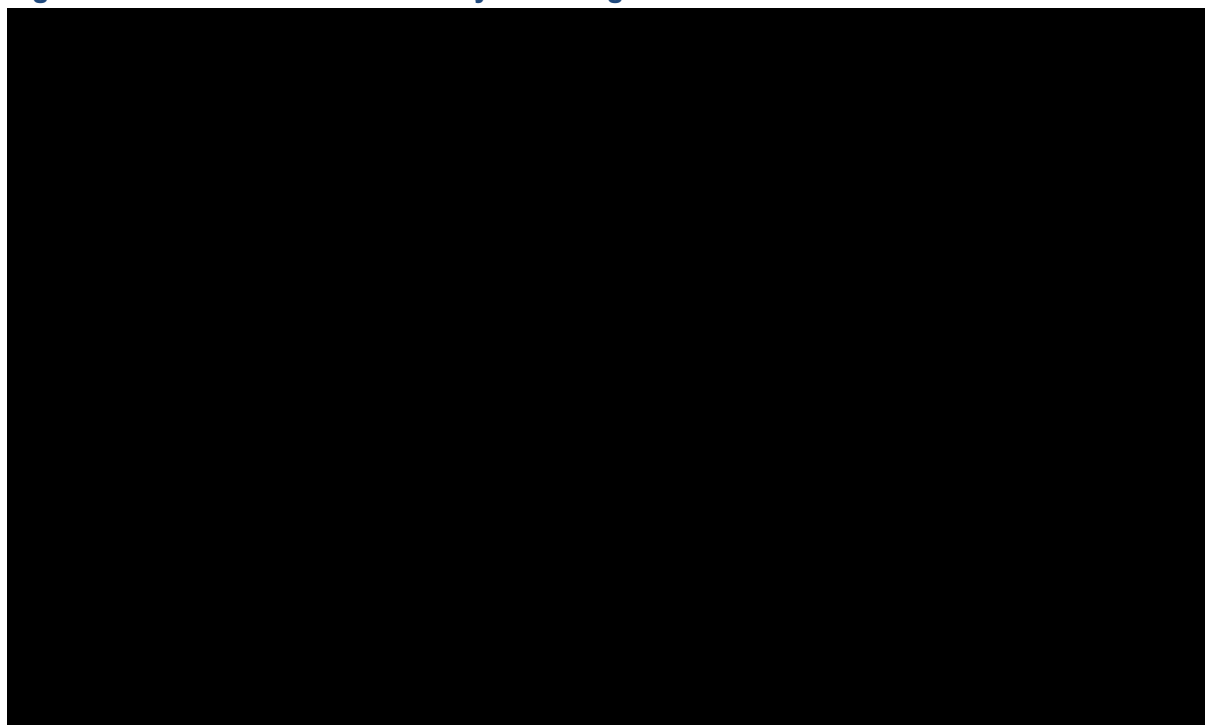
- e) Specify in more detail the chosen model (e.g., random intercept/slope) and its fixed and random structure.

I. To investigate the fixed part:

- i. Please plot the mean profile of EQ-5D-5L collected from APPEAR-C3G over the available time points, differentiated by CKD stage (please also keep CKD stage 1 and 2 separate).

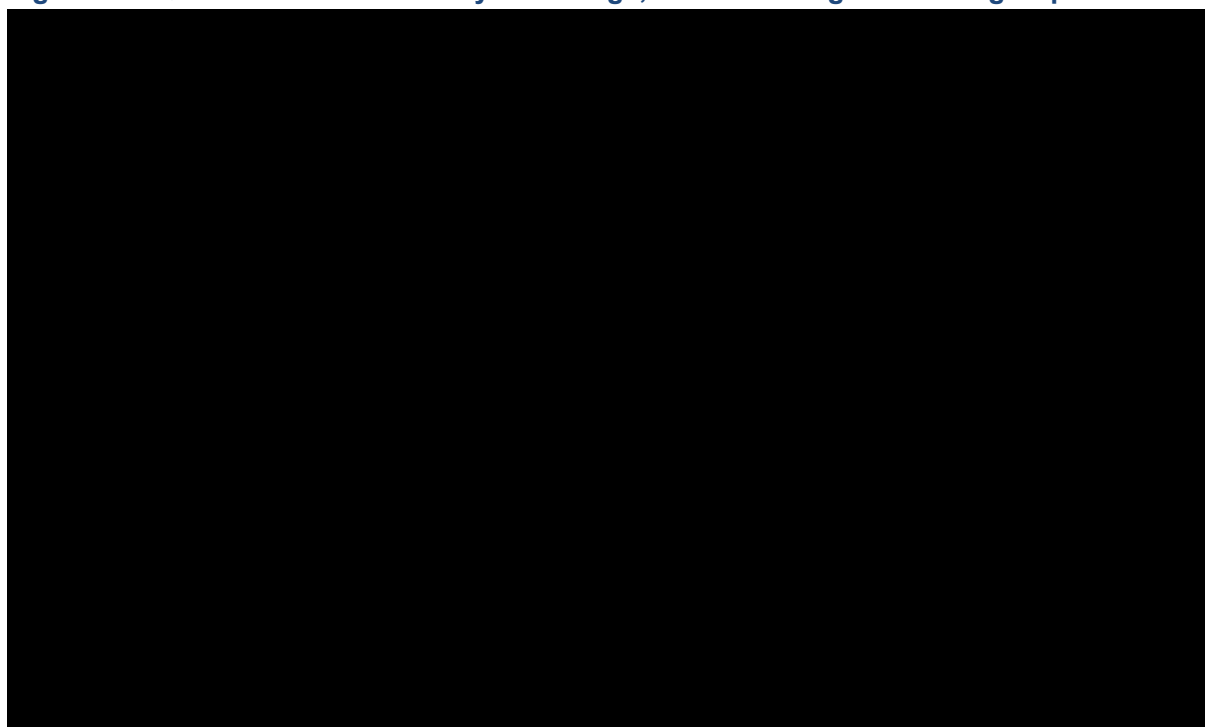
Figure 4 presents the mean EQ-5D score by visit and CKD stage, while Figure 5 presents the data with CKD stages 1 and 2 grouped. For CKD stage 4 it should be noted that overall only 16 EQ-5D measurements were available from the APPEAR-C3G trial (see CS Table 40).

Figure 4: EQ-5D scores over time by CKD stage



Abbreviations: CKD, chronic kidney disease

Figure 5: EQ-5D scores over time by CKD stage, with CKD stages 1 and 2 grouped



Abbreviations: CKD, chronic kidney disease

- ii. Please justify whether the linearity and normality assumptions are not violated.

Figure 6 presents a histogram of residuals, with a normal distribution density function overlaid on the graph. Figure 7 presents the quartile-normal plot of the residuals.

Figure 6: Histogram of residuals

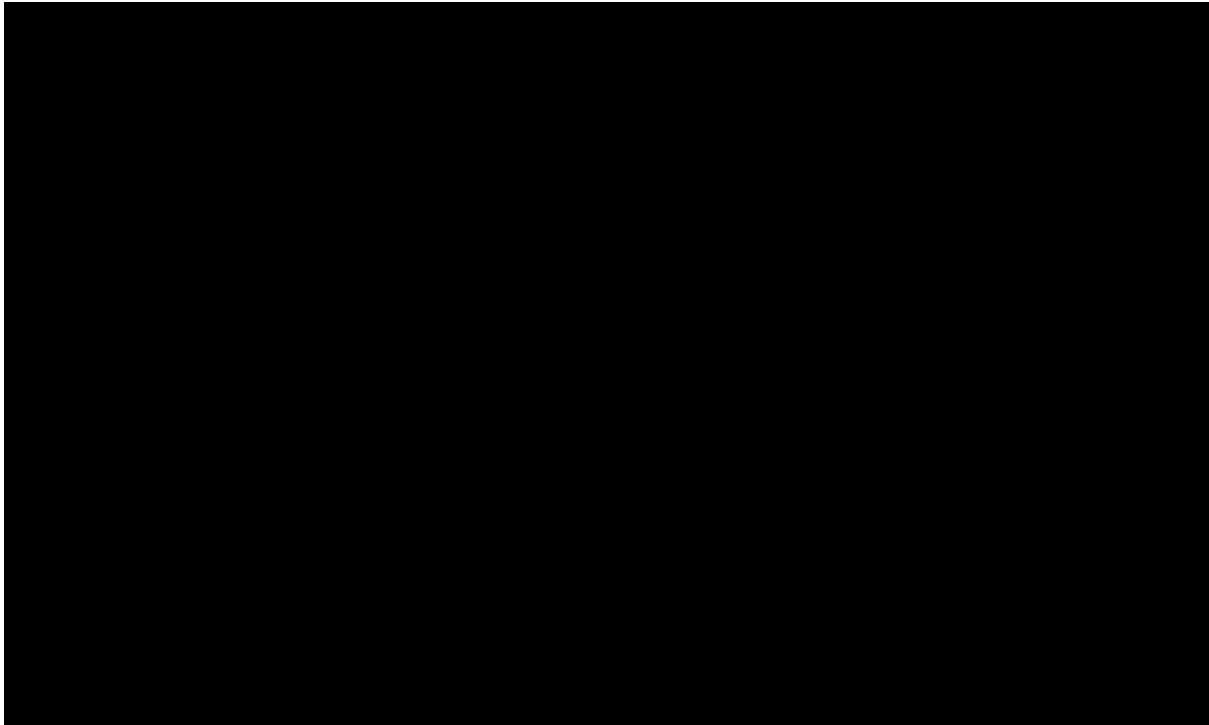


Figure 7: Quartile-normal plot

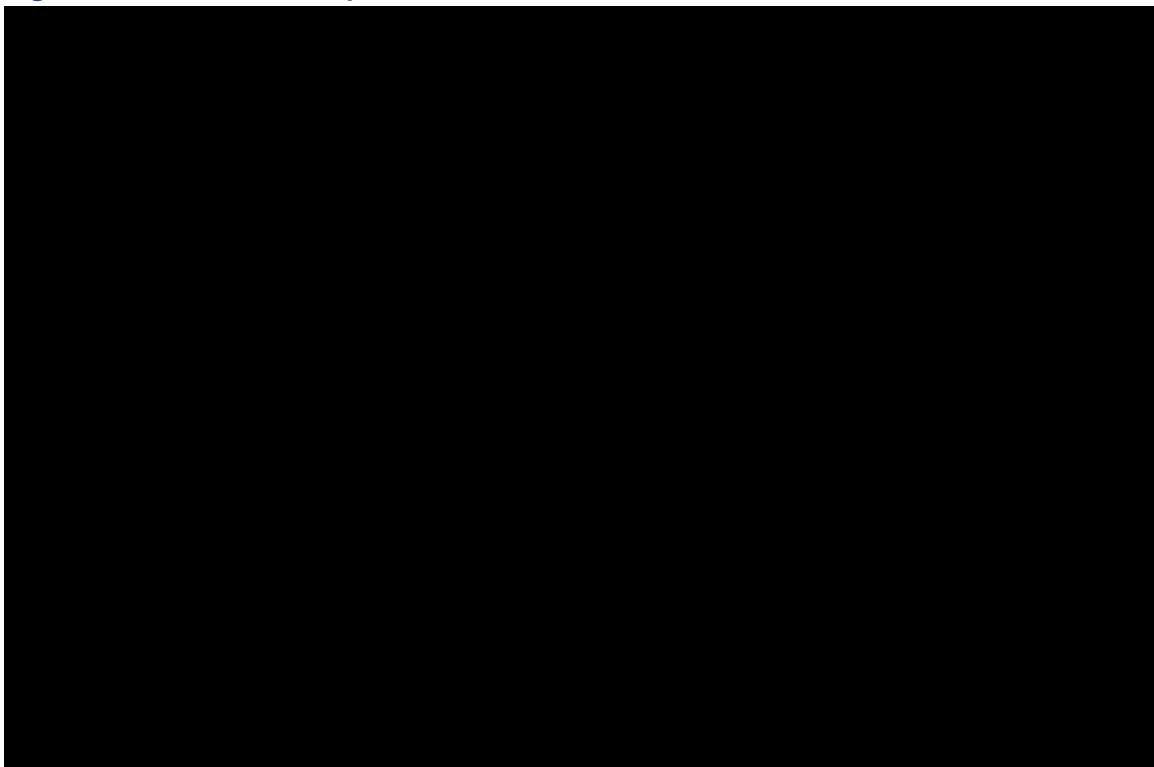


Figure 8 and Figure 9 present the component-residual plots for the continuous variables included in the model, age and baseline EQ-5D, including a smoothed curve of the points represented in green. In the plot of age, the smoothed line does not deviate significantly from the linear line, and so a linear relationship with age is expected to be appropriate. In the plot for baseline EQ-5D, the smoothed line follows the linear line well, with deviation from linear only in the tail where there is an outlier individual with a very low baseline utility. Overall, this does not appear to deviate significantly from the assumption of linearity.

Figure 8: Component-residual plot for age

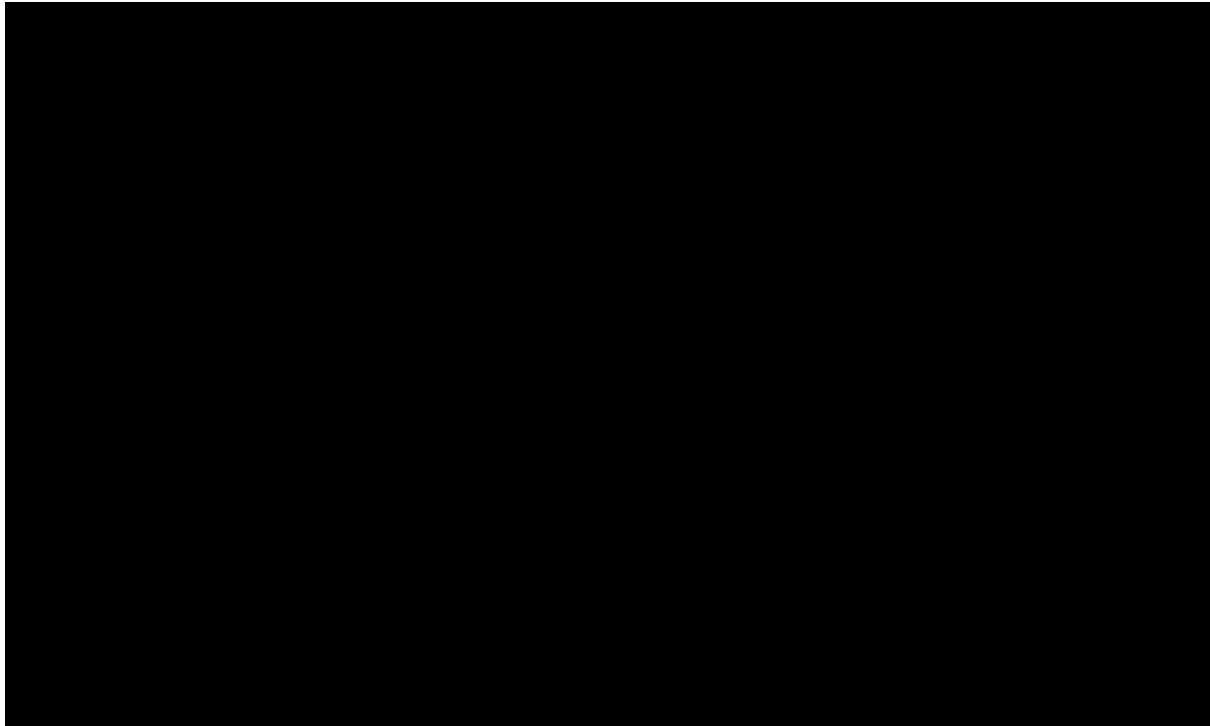
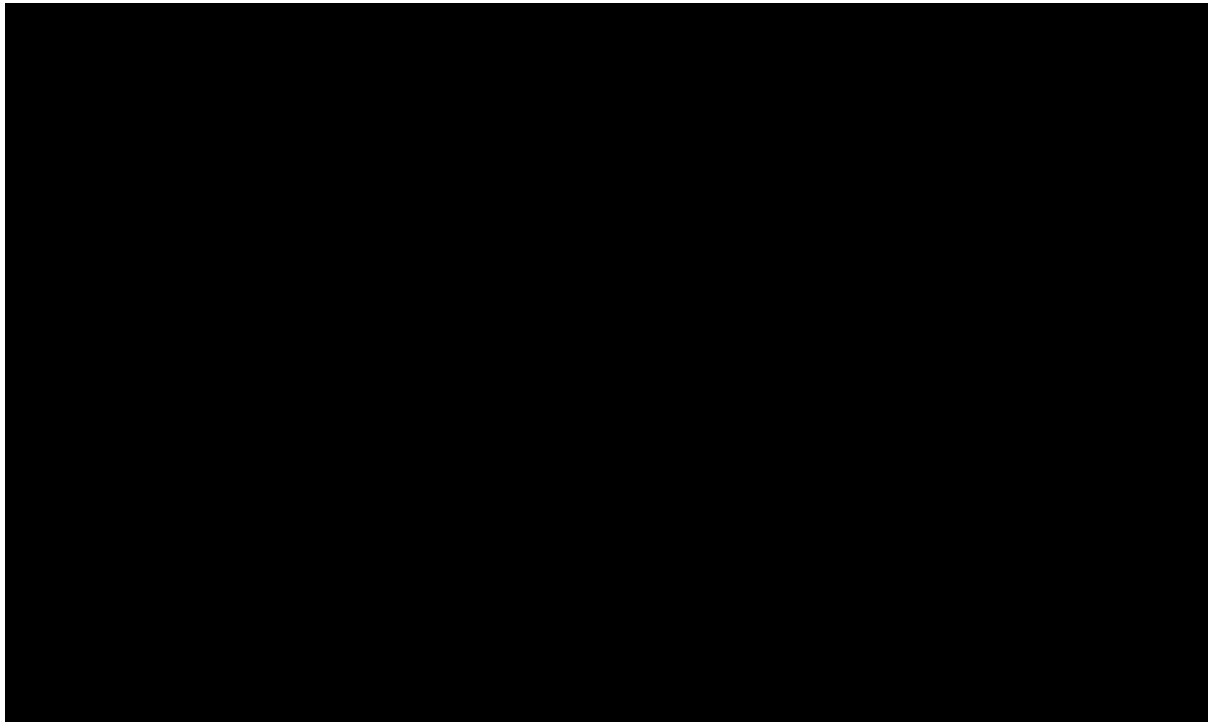


Figure 9: Component-residual plot for baseline EQ-5D



iii. Please explain the covariate selection process.

Covariates considered in the regression model included CKD stage, age, sex and baseline EQ-5D. CKD stage was included as this is used to define the economic model health states; however, in the regression model that treated CKD stages 1 and 2 as separate, the predicted utility value for CKD stage 2 was higher than for CKD stage 1, which was not deemed clinically plausible. As such, CKD stages 1 and 2 were combined, as outlined in the CS (see Section 3.4.1).

Age and sex were included to account for any imbalances across health states, as they are known predictors of HRQoL. Similarly, baseline EQ-5D was included in the model to address any imbalances in EQ-5D at baseline. While age was not significant in the model (see CS Table 41), as it is a known predictor of HRQoL it was retained in the final model, as patients in CKD stage 1 were younger than those in other stages.

Treatment allocation was also considered as a covariate in the model; however this was not associated with a significant impact on HRQoL ($p=$ [REDACTED]) and so was not incorporated into the final model. No further covariates were considered for the model, as the sample size from APPEAR-C3G was small, and CKD stage, age and sex were considered the most relevant determinants of HRQoL for the model.

Table 28 presents the outputs of two models that only include CKD stage as covariates. Model 1 includes CKD stages 1 to 4 separately; Model 2 combines CKD stages 1 and 2.

Table 28: Outputs of mixed effects models with only CKD stage as a covariate

	Model 1 – By individual CKD stage				Model 2 – Pooled CKD stages 1 and 2			
	Coefficient	S.E	LCI	UCI	Coefficient	S.E	LCI	UCI
CKD stage 2	████	████	████	████				
CKD stage 3	████	████	████	████	████	████	████	████
CKD stage 4	████	████	████	████	████	████	████	████
Constant	████	████	████	████	████	████	████	████

Abbreviations: CKD, chronic kidney disease; LCI, lower confidence interval; S.E., standard error; UCI, upper confidence interval

- iv. Please discuss the relevance of including potential interaction terms, e.g. time and CKD stage.

No interaction terms were considered, due to the small sample size in APPEAR-C3G. Table 29 presents the outputs of a model including interaction terms for CKD stage and visit.

Table 29: Mixed effects model including interaction terms for CKD stage and visit

	Coefficient	S.E.	LCI	UCI
CKD stage vs 1/2				
CKD stage 3	████	████	████	████
CKD stage 4	████	████	████	████
Visit				
Day 14	████	████	████	████
Day 30	████	████	████	████
Day 90	████	████	████	████
Day 180	████	████	████	████
Day 210	████	████	████	████
Day 270	████	████	████	████
Day 360	████	████	████	████
CKD stage and visit				
Day 14 CKD stage 3	████	████	████	████
Day 30 CKD stage 3	████	████	████	████
Day 90 CKD stage 3	████	████	████	████
Day 180 CKD stage 3	████	████	████	████
Day 210 CKD stage 3	████	████	████	████
Day 270 CKD stage 3	████	████	████	████
Day 360 CKD stage 3	████	████	████	████
Day 14 CKD stage 4	████	████	████	████
Day 30 CKD stage 4	████	████	████	████
Day 90 CKD stage 4	████	████	████	████
Day 180 CKD stage 4	████	████	████	████
Day 210 CKD stage 4	████	████	████	████
Day 270 CKD stage 4	████	████		
Day 360 CKD stage 4	████	████	████	████

	Coefficient	S.E.	LCI	UCI
Baseline EQ-5D	████	████	████	████
Age	████	████	████	████
Sex	████	████	████	████
Constant	████	████	████	████

Abbreviations: CKD, chronic kidney disease; LCI, lower confidence interval; S.E., standard error; UCI, upper confidence interval

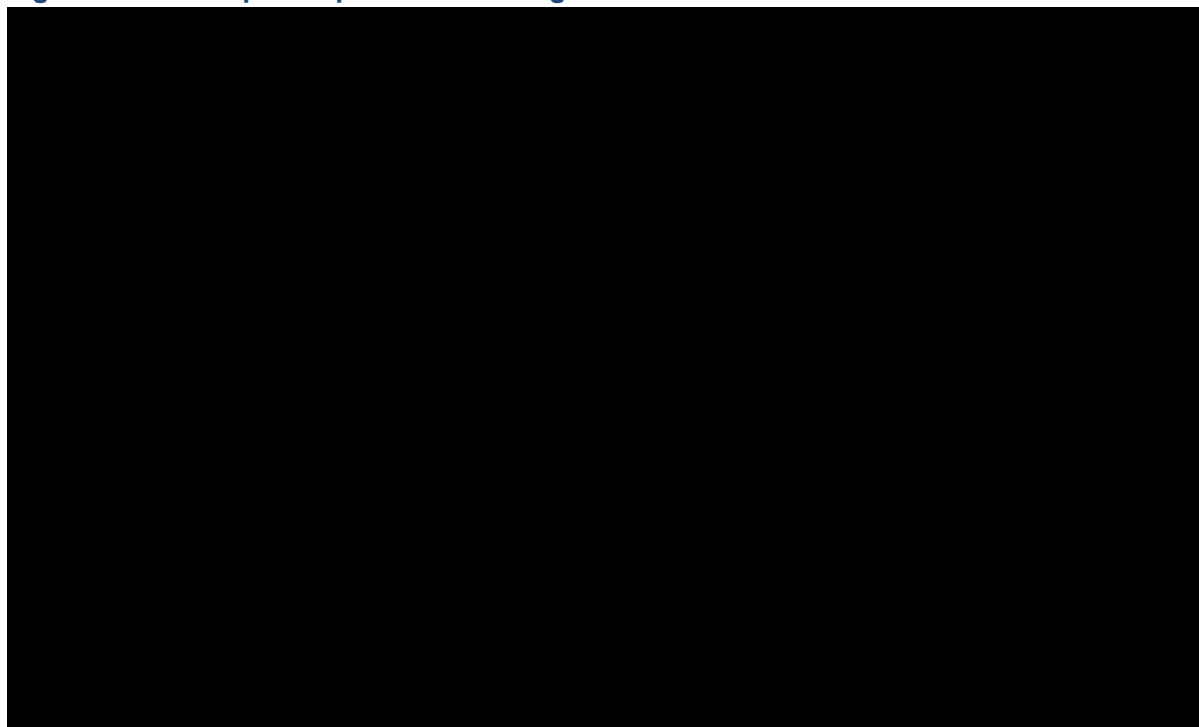
- I. To investigate the random part:
 - i. Please explain the selection process of the variance-covariance structure.

As outlined in response to question a), a mixed effects model with a random intercept for subject was selected to account for correlation in EQ-5D scores for each subject.

- ii. Please provide a plot of the subject-specific profiles of EQ-5D-5L collected from APPEAR-C3G over the available time points, differentiated by CKD stage (please also keep CKD stage 1 and 2 separate).

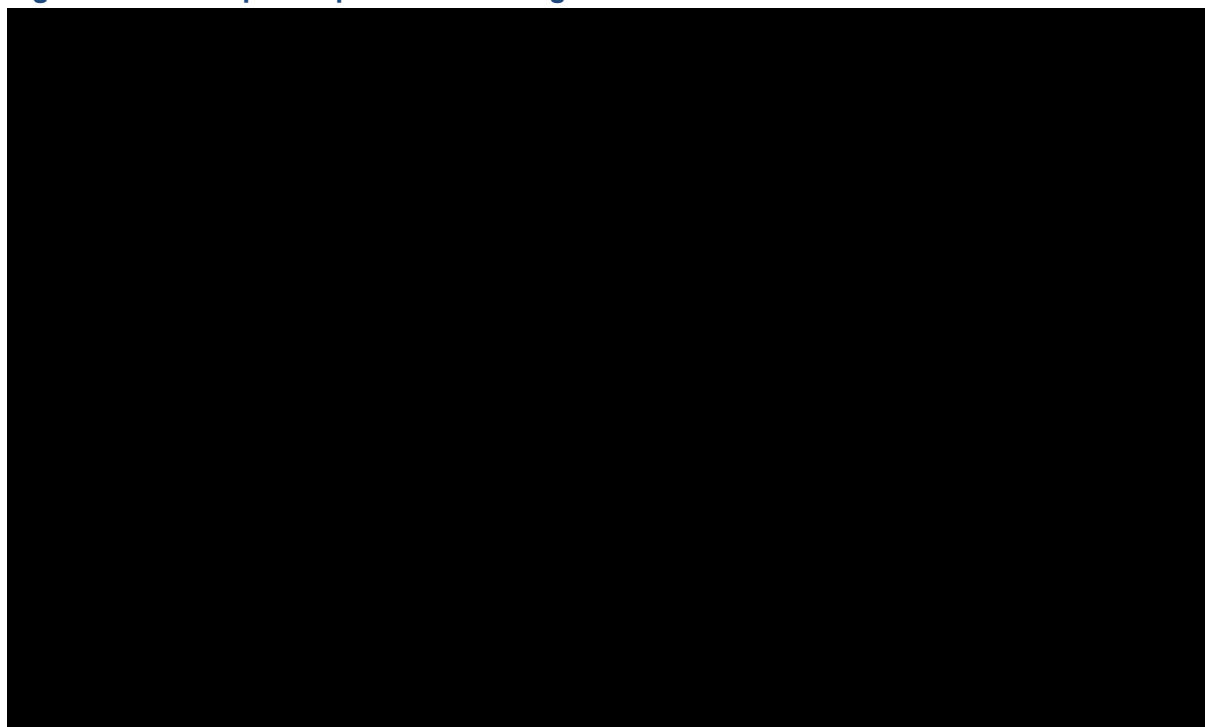
The requested plots are provided below in Figure 10 to Figure 14.

Figure 10: EQ-5D profile plot for CKD stage 1



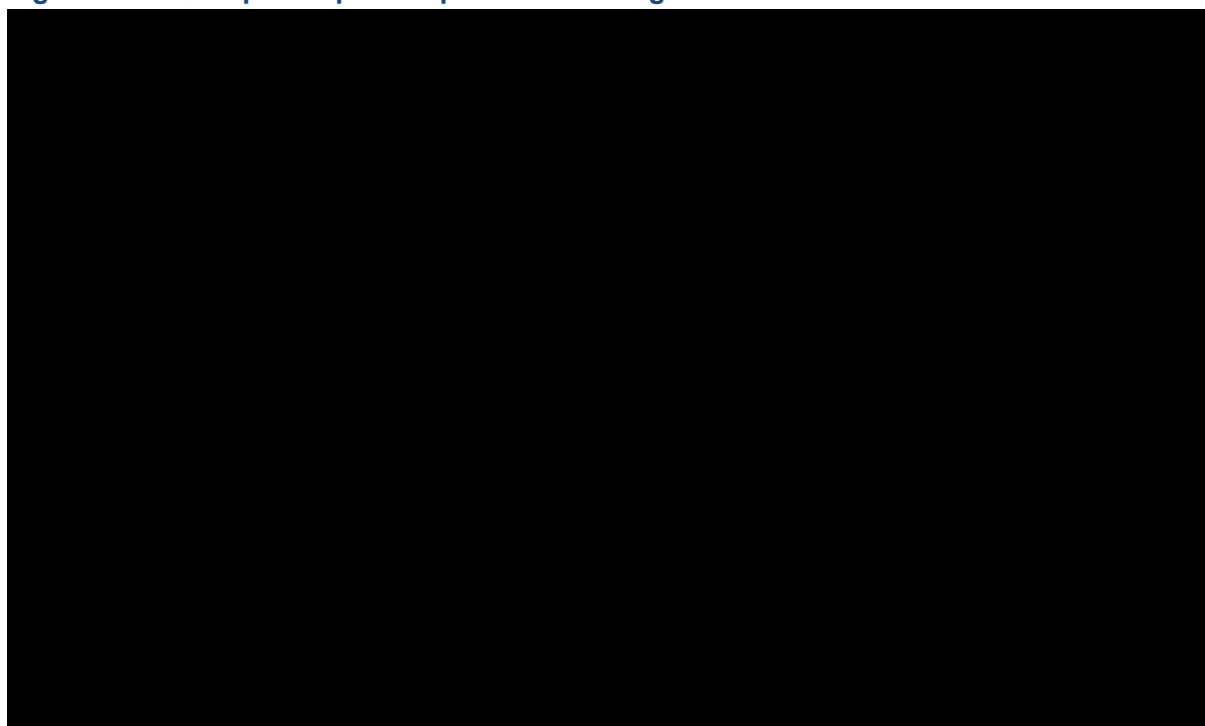
Abbreviations: CKD, chronic kidney disease

Figure 11: EQ-5D profile plot for CKD stage 2



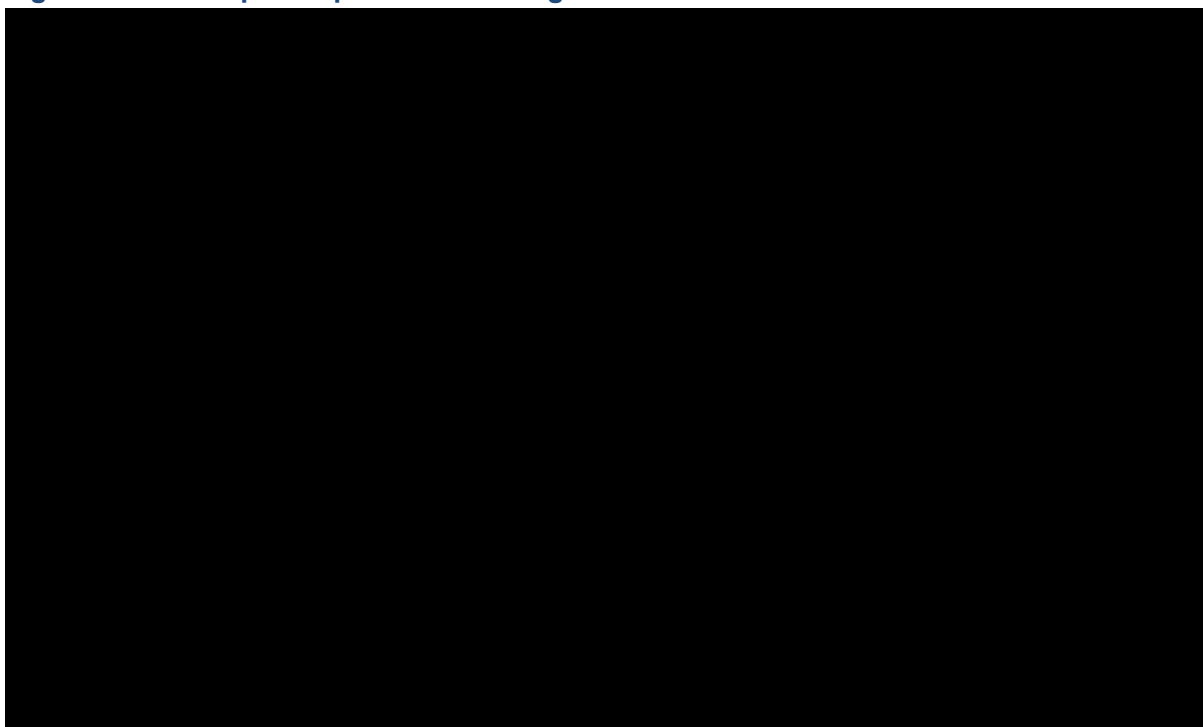
Abbreviations: CKD, chronic kidney disease

Figure 12: EQ-5D profile plot for pooled CKD stages 1 and 2



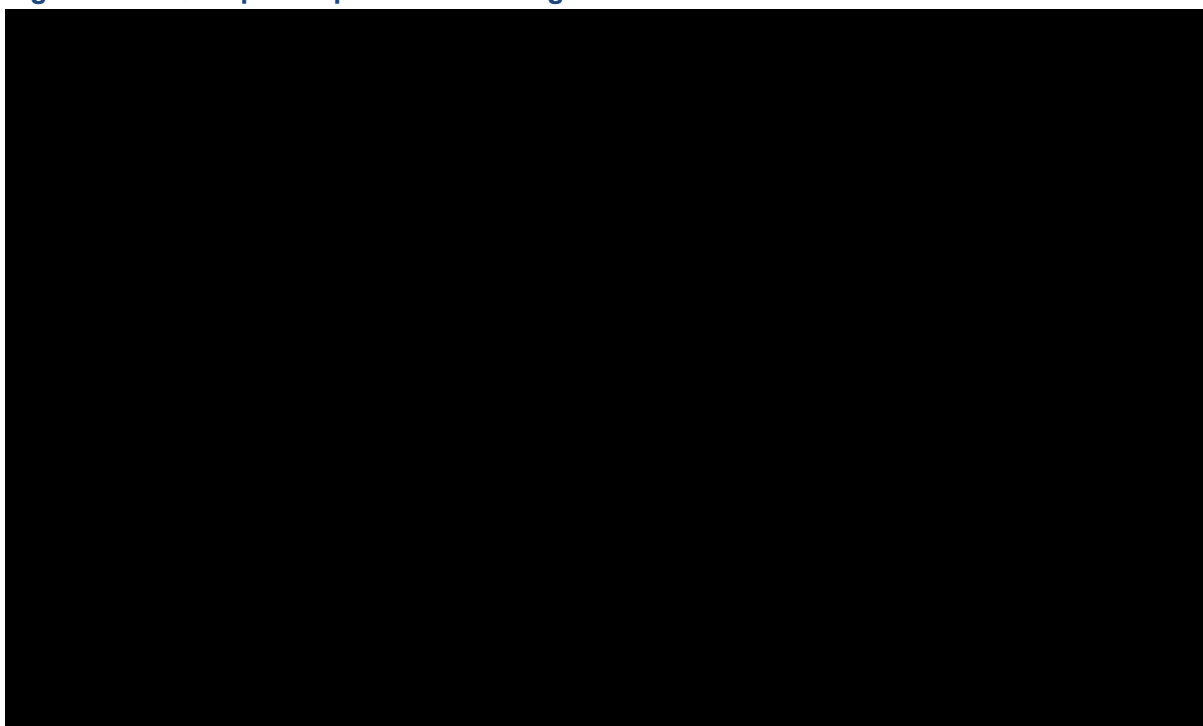
Abbreviations: CKD, chronic kidney disease

Figure 13: EQ-5D profile plot for CKD stage 3



Abbreviations: CKD, chronic kidney disease

Figure 14: EQ-5D profile plot for CKD stage 4



Abbreviations: CKD, chronic kidney disease

B 12. Priority question. For CKD stages 1 to 4, utility values were informed by EQ-5D-5L data from the APPEAR-C3G study.

- a) Please discuss the representativeness of the utility values derived from the APPEAR-C3G study for the adult C3G patient population, considering available literature and other evidence.

UK clinicians participating in an advisory board confirmed that the APPEAR-C3G trial population was reflective of C3G patients who would be anticipated to receive iptacopan in UK clinical practice.⁴ Therefore, utility values derived from EQ-5D-5L collected in the APPEAR-C3G trial can generally be considered representative for the modelled population.

To confirm the most suitable utility values for parameterising the economic model, Novartis discussed several options (all derived from EQ-5D) with a UK clinician and a UK health economist during a validation call:⁵

- Option 1: APPEAR-C3G trial data, based on regression model 1 (with separate CKD stages 1 and 2; see CS Table 41)
- Option 2: APPEAR-C3G trial data, based on regression model 2 (with CKD stages 1+2 pooled; see CS Table 41)
- Option 3: Adelphi DSP C3G (Lafayette et al. 2024)⁶²
- Option 4: Jesky et al. 2016⁶³

Details on these options are presented below in Table 30.

Table 30: Pre-KRT utility values considered for the economic analysis

	Trial data: APPEAR-C3G – Option 1	Trial data: APPEAR-C3G – Option 2	Adelphi DSP C3G (Lafayette et al. 2024)⁶⁴	Jesky et al. 2016⁶³
Population	Patients with C3G, mean age (SD)=27.9 (10.68), 36.5% female, n=74 (overall 484 observations)		Patients with C3G, median age (IQR)=41.5 (35–56), 37% female, n=100	Pre-dialysis CKD patients, median age (IQR)=64 (50–76), 39.2% female, n=745
Methodology	Data were collected in 18 countries (including the UK) from July 2021 to May 2024. EQ-5D-5L data mapped to EQ-5D-3L using the NICE recommended mapping algorithm. ⁶⁵ Utilities estimated using mixed-effects linear model 1 (Option 1) and 2 (Option 2)		Data were collected in France, Germany, Italy, Spain, China, Japan and the US from August 2022 to April 2023. EQ-5D-5L data mapped using the US tariff	Data were collected in the UK from October 2010 to March 2014. EQ-5D-3L data converted to EQ-5D index using a UK tariff ⁶⁶
Health state utility values				
CKD stage 1	0.91 (n=286)*	0.91 (n=394)*	0.67 (n=16)	0.85 (n=29) / Age-adjusted: 0.92
CKD stage 2	0.92 (n=108)*		0.77 (n=35)	
CKD stage 3A	0.87 (n=74)*	0.86 (n=74)*	0.80 (n=21)	0.80 (n=45) / Age-adjusted: 0.89
CKD stage 3B			0.70 (n=13)	0.80 (n=173) / Age-adjusted: 0.89
CKD stage 4	0.86 (n=16)*	0.85 (n=16)*	0.58 (n=15)	0.74 (n=423) / Age-adjusted: 0.82
CKD stage 5	NA	NA		0.73 (n=75) / Age-adjusted: 0.81

Footnotes: * Number of observations. Age-adjusted utility values for C3G population with baseline age of 27.9 years, 36.5% female²

Abbreviations: Age-adj, age-adjusted; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; DSP, Disease Specific Programme; EQ-5D-XL, EuroQol 5-dimensions X-levels; IQR, interquartile range; KRT, kidney replacement therapy; NA, not available; UK, United Kingdom; US, United States.

Sources: Lafayette et al. 2024;⁶⁴ Jesky et al. 2016;⁶³ Hernández-Alava et al. 2022;⁶⁵ Oppe et al. 2007.⁶⁶

In the discussion with advisors,⁵ it was noted that utility values generated from APPEAR-C3G using regression model 1 resulted in CKD stage 2 having a slightly higher utility value (0.92) than CKD stage 1 (0.91). Combining CKD stages 1 and 2 in regression model 2 resolved this implausibility. Utility values generated from the Adelphi DSP (as reported by Lafayette et al. 2024) also reflected data from patients with C3G;⁶⁴ however, the number of observations was substantially smaller than the number of observations in APPEAR-C3G, and utility values were considered implausible (for example, the CKD stage 3A utility value was higher than CKD stages 1 and 2; see Table 30). In addition, utilities were generated using a US tariff. Jesky et al. 2016 was not specific to patients in C3G but a study in general CKD, with a substantially older population.⁶³

Advisors agreed that APPEAR-C3G option 2 was appropriate to inform utility values for CKD stages 1–4. In the absence of data from APPEAR-C3G for people in CKD stage 5, advisors suggested using data from Jesky et al. 2016 to inform the utility value for CKD stage 5 (pre-KRT).⁵

Based on these discussions, data from APPEAR-C3G are considered an appropriate and representative source for utility data used within the model base case. A scenario analysis (presented in the CS) used utility values for CKD stages 1-5 from Jesky et al. 2016.

- b) Please justify pooling CKD stage 1 and 2 instead of keeping them separate, especially since they represent the stages with the highest number of measurements. Please discuss the possibility that later stage measurements are implausibly high.

In the APPEAR-C3G data, the observed mean utility value for CKD stage 1 (0.883) was deemed implausible, since it was lower than the mean utility value for CKD stage 2 (0.926) (see CS Table 40). A mixed effects linear model for repeated measures fit to the data also resulted in a slightly higher utility value for CKD stage 2 (0.92) than for CKD stage 1 (0.91), though the difference was not statistically significant (see CS Table 41). Pooling utility values for CKD stages 1 and 2 in the utility regression model led to a plausible pattern of utility values by CKD stage (see CS Table 41 and Table 43).

Several precedents for pooling utility values across CKD stages 1 and 2 exist; in fact, all previous NICE appraisals in CKD which required utility values for CKD stages 1 and 2 used the same utility values for both health states, as outlined below

- TA942²⁷, TA937²⁸ and TA623⁶⁷ used utility values as reported by Jesky et al. 2016, which pooled CKD stages 1 and 2 when deriving utility values (refer to Table 3 in the publication, 'Stage G1/G2')⁶³
- TA358²⁶ used utility values as reported by Gorodetskaya et al. 2005, which pooled CKD stages 1 and 2 when deriving utility values (refer to Table 2 in the publication, 'GFR ≥60')⁶⁸
- TA877⁵³ and T775²⁹ derived utility values for use in the appraisal from the respective trial data, pooling CKD stage 1 and 2 values in the utilised regression model

Details on the utilities used in these appraisals, along with other previous NICE appraisals in CKD as identified in a targeted literature review (TLR), are presented in Table 11 of Appendix F of the CS.

With regards to a possibility that utility values for later CKD stages are implausibly high, this was not a concern raised during validation of the utility values with experts.⁵ After adjusting utility values reported by Jesky et al. 2016⁶³ to the age and gender distribution of the APPEAR-C3G population (as described in CS Section 3.4.4.1), utility values were similar to the utility values generated from APPEAR-C3G data (see Table 31 below). A scenario analysis included in the CS used the Jesky et al. 2016 utility values for CKD stages 1–5 and was associated with a small improvement of the ICER (██████ with updated model; see Table 51).

Table 31: CKD stage 1–5 health state utility values used in the economic model

Health state	APPEAR-C3G	Jesky et al. 2016 ⁶³ (adjusted to age and sex of APPEAR-C3G population)
CKD stage 1	0.91	0.92
CKD stage 2	0.91	0.92
CKD stage 3a	0.86	0.89
CKD stage 3b	0.86	0.89
CKD stage 4	0.85	0.82
CKD stage 5 (pre-KRT)	N/A	0.81

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; N/A, not available.

Sources: Jesky et al. 2016.⁶³

- c) Please discuss the plausibility of the reported, relatively high utility values for the study population, especially in earlier CKD stages when compared to the UK age- and sex-matched general population utility for the study population (CS Table 43).

Early stages of CKD tend to be associated with a limited impact on HRQoL. As noted in the response to question B12 b), the utility values derived from APPEAR-C3G were similar to those reported in Jesky et al. 2016,⁶³ after adjusting for age differences between the populations; therefore supporting the plausibility of the APPEAR-C3G utility values used in the economic model base case.

B 13. The CS used age adjustments in the economic model to address “differences between the source population’s age for literature-based utility values and the baseline of the modelled population”. This is particularly relevant since the CS population is substantially younger (baseline mean age in economic model: 27.9 years) than those in the studies identified in the HRQoL literature review.

- a) The study by Lee et al. (2005) informed dialysis and post-transplant health state utilities in the base case, with patients aged between 51.6 years and 64.3 years at time of survey completion, causing relatively low dialysis and post-transplant utilities when compared to prior CKD stages. Please discuss the validity of the utility values from Lee et al. (2005), especially in terms of comorbidities apparent in later ages and the remark by the clinical advisor, considering the post-transplant health state “relatively low” and supporting alternatively the use of Liem et al.’s value (2008) (CS, Clinical and Model Validation for Iptacopan in C3G).

KRT is associated with a considerable impact on HRQoL, including from significant potential complications. Dialysis is associated with fatigue, hypotension (low blood pressure), itchy skin and muscle cramps.⁶⁹ Kidney transplantation is associated with multiple short-term risks including surgical complications, bleeding, post-transplant infection, and acute rejection of the transplanted kidney.⁷⁰ The longer-term risks of transplants similarly include infections, organ rejection, and recurrent disease,^{70, 71} which is particularly apparent in C3G. Kidney transplant recipients may also experience significant side effects and risks associated with long-term use of immunosuppressive regimens to prevent graft rejection, such as increased risk of cancer.⁷⁰⁻⁷³ As well as the negative HRQoL impacts of these complications, the independence of people with C3G is limited with dialysis a very time-consuming treatment which puts a burden on the daily life for patients, their families and carers.^{37, 74, 75}

The utility values from Lee et al. 2005 are considered appropriate, as they reflect the impact of KRT on HRQoL in a UK population (N=416) using EQ-5D-3L and a UK tariff.⁷⁶ Lee et al. 2005 utilities for dialysis and post-transplant health states were used in seven previous NICE appraisals in various chronic kidney diseases (see Table 34), including a recent appraisal in IgA nephropathy (TA937), which also affects a younger population.²⁸

To account for the differences between the population's age in the Lee et al. 2005 study and the baseline age of the modelled population, the utilities used in the model were age-adjusted (see CS Section 3.4.4.1 for further details). Therefore, it is expected that the impact of the different population ages in Lee et al. 2005 versus the population in the CS would be limited, with age-adjustments accounting for differences in age-related comorbidities.⁷⁶ The approach for age adjustments was also validated with a UK health economist.⁵

While the clinical advisor stated that the post-transplant utility value from Lee et al. 2005 was relatively low, they also highlighted expected variation in HRQoL between patients, since not all patients have good outcomes following a transplant; for example, some patients experience surgical complications.⁵

As requested by the EAG, a scenario analysis is provided using the post-transplant utility value from Liem et al. 2008,⁷⁷ with results in Table 32 showing an increase in the ICER by [REDACTED]. Liem et al. 2008 was considered as potential source for utilities during development of the CS, but validation with clinical and health economic experts highlighted that its methodology (a meta-analysis of EQ-5D-based utility values reported across multiple international studies which did not consistently provide information on the value sets used) introduced significant uncertainty.^{5, 77} Experts therefore preferred using utility values from Lee et al. 2005, as it was a UK study.⁵

Table 32: Scenario analysis results: Alternative post-transplant utilities

Extrapolation	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			% change in ICER versus revised base case
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	
Revised company base case (Lee et al. 2005 post-transplant utilities) ⁷⁶	██████	16.88	£355,162	15.13	██████	1.74	██████	N/A
Scenario analysis using Liem et al. 2008 post-transplant utilities ⁷⁷	██████	17.18	£355,162	15.70	██████	1.49	██████	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Sources: Lee et al. 2005;⁷⁶ Liem et al. 2008.⁷⁷

- b) Please provide reference number 8 based on Adelphi DSP, “Lafayette R, Sidhu R, Proudfoot C, et al. WCN24-1688 SELF-REPORTED QUALITY OF LIFE IN COMPLEMENT 3 GLOMERULOPATHY PATIENTS DELINEATED BY CKD STAGE: A REAL-WORLD, MULTI-COUNTRY SURVEY. *Kidney International Reports* 2024;9:S60-S61”.

The requested file has been provided in the reference pack ‘References_Publications_v2.zip’ submitted through NICE Docs on 21st March 2025 (file name ‘Lafayette 2024_Self-reported QoL.pdf’; reference number 8 in the subsequently provided requested numbered reference pack). Information about the study, as one of two relevant studies identified in the C3G-specific utilities SLR, is also summarised in Appendix F.

Whilst EQ-5D-5L data were collected as part of the Adelphi DSP, providing utilities for CKD stages 1–4/5, these were not considered clinically plausible,⁵ since CKD stage 1 patients had the worst HRQoL after patients with CKD stage 4/5 (utility values for CKD stage 1: 0.67; 2: 0.77; 3a: 0.80; 3b: 0.70; 4/5: 0.58).⁶² Sample sizes per CKD stage were small (ranging from 13 patients in CKD stage 3b to a maximum of 35 patients in CKD stage 2),⁶² which may have led to implausible results. In addition, the study used a US tariff to generate utility values.⁶² Therefore, the utility values were deemed unsuitable for use in the model.

- c) In Sinha et al. and its supplement, it is apparent that EQ-5D-5L was analysed from Adelphi DSP, and data are available to differentiate by disease stage (including stage 5) as well as between patients receiving regular dialysis and those who have received a kidney transplant. Please explain why these data have not been used for cross-validation of health state utilities.

This is the same study as that referred to in B13 b). Lafayette et al. 2024 was a congress abstract;⁶² Sinha et al. is a submitted manuscript (Novartis data on file).⁷⁸ The submitted manuscript only reports EQ-5D utility values for eGFR <30 mL/min/1.73m² and >30 mL/min/1.73m², but not by CKD stage. In addition, the limitation that a US tariff was used remains. Therefore, the submitted manuscript was not considered to provide suitable data for cross-validation of utility values.

- d) Please provide a table of all identified TAs and studies which report HRQoL, specifying the respective CKD variant and mean age of the study population. Please also report utility values and sample size per CKD stage.

NICE technology appraisals (TAs) in chronic kidney diseases with final guidance published in the last 10 years were reviewed in a TLR conducted in December 2024 and summarised in the CS and its appendices (see response to B26 for further details). The utility results of the TLR have been reproduced here for convenience. Overall, 13 TAs met the eligibility criteria and were included in the TLR. While all 13 TAs reported utility values for health states of interest, some TAs only reported utilities for CKD stages prior to KRT, and some only reported utilities for KRT (dialysis/transplant). Table 33 summarises the utility sources and values for pre-KRT CKD stages. Table 34 presents utility sources and values for KRT. Mean age of the study population as well as sample size per CKD stage were not included in the original tables presented in the CS appendices but are now added in the column ‘Study characteristics for source of utility data’.

Table 33: Utilities in previous NICE technology appraisals in chronic kidney diseases – CKD stages pre-KRT

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
TA942 (2023) ²⁷	Adults with CKD	G+90_A-30	0.850	HSUV	Jesky et al. 2016 ⁶³	Overall: N=745; Per CKD stage: CKD stage 1–2: n=29; CKD stage 3a: n=45; CKD stage 3b: n= 173; CKD stage 4: n= 423; CKD stage 5: n= 75. Median (IQR) age: 64 (50–76) years		–
		G+90_A-300	0.850					
		G+90_A+300	0.850					
		G+60_A-30	0.850					
		G+60_A-300	0.850					
		G+60_A+300	0.850					
		G+45_A-30	0.800					
		G+45_A-300	0.800					
		G+45_A+300	0.800					
		G+30_A-30	0.800					
		G+30_A-300	0.800					
		G+30_A+300	0.800					
		G+15_A-30	0.740					
		G+15_A-300	0.740					
		G+15_A+300	0.740					
		G-15_A-30	0.730					
		G-15_A-300	0.730					
		G-15_A+300	0.730					
TA937 (2023) ²⁸	Adults with primary IgAN at risk of rapid disease progression with a UPCR ≥ 1.5 g/g	CKD stage 1	0.850	HSUV	Jesky et al. 2016 ⁶³ reported in published SLR: Cooper et al. 2020)	Overall: N=745; Per CKD stage: CKD stage 1–2: n=29; CKD stage 3a: n=45; CKD stage 3b: n= 173; CKD stage 4: n=		The Committee commented that health state utility values were aligned with TA775
		CKD stage 2	0.850					
		CKD stage 3a	0.800					
		CKD stage 3b	0.800					

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
		CKD stage 4	0.740			423; CKD stage 5: n=75. Median (IQR) age: 64 (50–76) years		
		CKD stage 5	0.730					
TA877 (2023) ⁵³	Adults with CKD and type-2 diabetes mellitus	CKD stage 1 & 2	0.771	HSUV	Pivotal trial (FIDELIO-DKD)	N=5,674 (not reported by CKD stage). Mean age: 65.6 years		EAG highlighted implausibility of CKD stage 3 utility being higher than CKD stage 1 & 2. Company amended CKD stage 1 & 2 utility to be the same as CKD stage 3. The Committee concluded that the utility values were appropriate.
		CKD stage 3	0.773					
		CKD stage 4	0.762					
		CKD stage 5 without KRT	0.742					
TA807 (2022) ⁷⁹	Adults with symptomatic anaemia associated with CKD who are not dialysis-dependent at the time of treatment initiation	CKD	0.033	Utility decrement	Ara & Brazier 2011 ⁸⁰	Respondents with kidney complaints: n=297; mean age: 52.7 years	Decrement calculated by subtracting utility reported in Ara & Brazier 2011 for people with kidney complaints from the general population utility	Committee preferred a multiplicative approach to implementing utility values in the model (vs additive approach in original company submission)
TA775 (2022) ²⁹	Adults with CKD	CKD stage 1	0.770	HSUV	Pivotal trial (DAPA-CKD)	Overall: N=4,304; Per CKD stage: CKD stage 1–2: n=454; CKD stage 3a: n=1,328; CKD stage 3b: n=1,898;		–
		CKD stage 2	0.770					
		CKD stage 3a	0.770					
		CKD stage 3b	0.770					

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
		CKD stage 4	0.760			CKD stage 4–5: n=624. Mean (SD) age: 61.8 (12.1)		
		CKD stage 5 (pre-KRT)	0.730					
TA623 (2020) ⁶⁷	Adults with CKD stage 3-4 with HK	CKD stage 3	0.800	HSUV	Jesky et al. 2016 ⁶³	Overall: N=745; Per CKD stage: CKD stage 1–2: n=29; CKD stage 3a: n=45; CKD stage 3b: n= 173; CKD stage 4: n= 423; CKD stage 5: n= 75. Median (IQR) age: 64 (50–76) years		–
		CKD stage 3B	0.800					
		CKD stage 4	0.740					
TA599 (2019) ³⁰	Adults with hyperkalaemia (HK) and an underlying condition of CKD or heart failure	CKD stage 3A	0.870	HSUV	Gorodetskaya et al. 2005 ⁶⁸	Overall: N=271; Per CKD stage: CKD stage 1–2: n=22; CKD stage 3a–b: n=51; CKD stage 4: n=66; CKD stage 5: n=132. Mean (SD) age: 62.8 (12.7)		Committee preferred utilities from Eriksson et al. 2016: CKD stage 3A: 0.85
		CKD stage 3B	0.870					Committee preferred utilities from Eriksson et al. 2016: CKD stage 3B: 0.85
		CKD stage 4	0.850					Committee preferred utilities from Eriksson et al. 2016: CKD stage 4: 0.81
		CKD stage 5 (pre-KRT)	0.570	HSUV	Lee et al. 2005 ⁷⁶	Overall: N=416; Pre-dialysis: n=34.		Committee preferred utilities from Eriksson et al. 2016: CKD stage 5 (pre-KRT): 0.74

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
						Mean age: 58.2 for males and 55.5 for females		(dialysis patients used as a proxy)
TA358 (2015) ²⁶	Adults with autosomal dominant polycystic kidney disease (ADPKD)	CKD stage 1 & 2	0.000	Disutility	Gorodetskaya et al. 2005 ⁶⁸	Overall: N=271; CKD stage 1–2: n=22. Mean (SD) age: 62.8 (12.7)	CKD stage 1 & 2 assumed equivalent to general population	Company also presented condition-specific HSUVs; Committee concluded that these HSUVs are unlikely to significantly alter the outcome
		CKD stage 3	0.030	Disutility	Gorodetskaya et al. 2005 ⁶⁸	Overall: N=271; CKD stage 3: n=51. Mean (SD) age: 62.8 (12.7)		
		CKD stage 4	0.050	Disutility	Gorodetskaya et al. 2005 ⁶⁸	Overall: N=271; CKD stage 4: n=66. Mean (SD) age: 62.8 (12.7)		
		CKD stage 5, pre-dialysis	0.222	Disutility	Lee et al. 2005 ⁷⁶	Overall: N=416; Pre-dialysis: n=34. Mean age: 58.2 for males and 55.5 for females		
		ESRD, conservative care	0.352	Disutility	Lee et al. 2005 ⁷⁶	Overall: N=416; Pre-dialysis: n=34. Mean age: 58.2 for males and 55.5 for females		

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody-associated vasculitis; ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; HK, hyperkalaemia; HSUV, health state utility value; IgAN, immunoglobulin A nephropathy; KRT, kidney replacement therapy; MTA, multi-technology appraisal; SLR, systematic literature review; TA, technology appraisal; UPCR, urine protein to creatinine ratio.

Sources: Jesky et al. 2016;⁶³ Cooper et al. 2020;⁸¹ FIDELIO-CKD;⁸² Ara and Brazier. 2011;⁸⁰ DAPA-CKD;⁸³ Gorodetskaya et al. 2005;⁶⁸ Lee et al. 2005.⁷⁶

Table 34: Utilities in previous NICE technology appraisals in chronic kidney diseases – KRT (dialysis / transplant)

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
TA942 (2023) ²⁷	Adults with CKD	Peritoneal dialysis	0.580	HSUV	Liem et al. 2008 ⁷⁷	Meta-analysis; Mean age across studies (for PD): 57.9		–
		Haemodialysis	0.560	HSUV	Liem et al. 2008 ⁷⁷	Meta-analysis; Mean age across studies (for HD): 60.4		
		Kidney transplant	0.710	HSUV	Lee et al. 2005 (as referenced in TA775)	Overall: N=416; Transplant: n=209. Mean age: 58.2 for males and 55.5 for females	For 1 st year of kidney transplant. Thereafter, G3A1 utility is applied, with immunosuppressive therapy disutility	
		Immunosuppressive therapy	0.010	Disutility (additive)	Peasgood et al. 2016 ⁸⁴	N=2,469; Mean age: 39.3	Disutility applied from 2 nd year post-transplant	
TA937 (2023) ²⁸	Adults with primary IgAN at risk of rapid disease progression with a UPCR $\geq$ 1.5 g/g	Haemodialysis	0.440	HSUV	Lee et al. 2005 (as reported in published SLR: Cooper et al. 2020)	Overall: N=416; HD: n=99. Mean age: 58.2 for males and 55.5 for females		The Committee commented that health state utility values were aligned with TA775
		Peritoneal dialysis	0.530	HSUV	Lee et al. 2005 ⁷⁶ (as reported in published SLR:	Overall: N=416; PD: n=74. Mean age: 58.2 for males and 55.5 for females		

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
					Cooper et al. 2020)			
		Post transplant	0.710	HSUV	Lee et al. 2005 (as reported in published SLR: Cooper et al. 2020)	Overall: N=416; Transplant: n=209. Mean age: 58.2 for males and 55.5 for females		
TA890 (2023) ⁸⁵	Adults with CKD-associated pruritus who are on haemodialysis	Transplant	0.712	HSUV	Lee et al. 2005 ⁷⁶ (as referenced in TA775)	Overall: N=416; Transplant: n=209. Mean age: 58.2 for males and 55.5 for females		–
TA882 (2023) ³¹	Adults with active lupus nephritis	Dialysis	0.485	HSUV	Lee et al. 2005 ⁷⁶	Overall: N=416; HD: n=99; PD: n=74. Mean age: 58.2 for males and 55.5 for females	Weighted average of utility for HD and PD (50:50)	EAG preferred utility from Cooper et al. 2020: HSUV of 0.69 (EAG own meta-analysis). Accepted by company. No comments from Committee
		Transplant	0.710	HSUV	Lee et al. 2005 ⁷⁶	Overall: N=416; Transplant: n=209. Mean age: 58.2 for males and 55.5 for females		EAG preferred utility from Li et al. 2017 (regression analysis): HSUV of 0.818 (for age 33.2 years and

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
								87.7% female). Accepted by company. No comments from Committee
TA877 (2023) ⁵³	Adults with CKD and type-2 diabetes mellitus	Dialysis, acute	0.711	HSUV	Pivotal trial (FIDELIO-DKD)	N=5,674 (not reported by CKD stage). Mean age: 65.6 years		Committee preferred HSUV from NICE NG28: 0.595
		Dialysis, post-acute	0.711	HSUV				Committee preferred HSUV from NICE NG28: 0.595
		Transplant, acute	0.734	HSUV				Committee preferred HSUV from NICE NG28: 0.748
		Transplant, post-acute	0.880	HSUV				Committee preferred HSUV from NICE NG28: 0.748
TA825 (2022) ⁸⁶	Adults with anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV)	Peritoneal dialysis	0.530	HSUV	Lee et al. 2005 ⁷⁶ (as referenced in NICE TA623)	Overall: N=416; PD: n=74. Mean age: 58.2 for males and 55.5 for females		–
		Haemodialysis	0.443	HSUV	Lee et al. 2005 ⁷⁶ (as referenced in NICE TA623)	Overall: N=416; HD: n=99. Mean age: 58.2 for males and 55.5 for females		

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
		Transplant	0.712	HSUV	Lee et al. 2005 ⁷⁶ (as referenced in NICE TA623)	Overall: N=416; Transplant: n=209. Mean age: 58.2 for males and 55.5 for females		
TA809 (2022) ⁸⁷	Adults with CKD awaiting a kidney transplant from a donor, who are highly sensitised	Haemodialysis	0.276	Utility decrement	Liem et al. 2008 ⁷⁷	Meta-analysis; Mean age across studies (for HD): 60.4	Decrements calculated by subtracting utilities reported in Liem et al. 2008 from the general population utility	Committee preferred utility values from Li et al. 2017 (used by company in a scenario analysis; values not reported)
		Peritoneal dialysis	0.263	Utility decrement	Liem et al. 2008 ⁷⁷	Meta-analysis; Mean age across studies (for PD): 57.9		
		Functioning graft	0.053	Utility decrement	Liem et al. 2008 ⁷⁷	Meta-analysis; Mean age across studies (for transplant): 51.4		
		Haemodialysis: caregiver	0.012	Utility decrement	Nagasawa et al. 2018 ⁸⁸	N=51 pairs of patient and caregivers. Mean (SD) age for patients: 67.7 (12.1); Mean (SD) age for caregivers: 64.5 (12.3)		EAG preferred carer disutility of 0.03 from Thomas et al. 2015. Accepted by company. No comments from Committee
TA807 (2022) ⁷⁹	Adults with symptomatic anaemia	Haemodialysis	0.352	Utility decrement	Lee et al. 2005 ⁷⁶ (as referenced	Overall: N=416; HD: n=99. Mean age: 58.2 for		Committee preferred a multiplicative

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
	associated with CKD who are not dialysis-dependent at the time of treatment initiation				in NICE TA358)	males and 55.5 for females		approach to implementing utility values in the model (vs additive approach in original company submission)
		Peritoneal dialysis	0.262	Utility decrement	Lee et al. 2005 ⁷⁶ (as referenced in NICE TA358)	Overall: N=416; PD: n=74. Mean age: 58.2 for males and 55.5 for females		
TA775 (2022) ²⁹	Adults with CKD	Dialysis	0.462	HSUV	Lee et al. 2005 ⁷⁶	Overall: N=416; HD: n=99; PD: n=74. Mean age: 58.2 for males and 55.5 for females	Weighted average of peritoneal dialysis utility (0.53; 24% of patients) and haemodialysis utility (0.44; 76% of patients)	–
		Transplant	0.710	HSUV	Lee et al. 2005 ⁷⁶	Overall: N=416; Transplant: n=209. Mean age: 58.2 for males and 55.5 for females		
TA623 (2020) ⁶⁷	Adults with CKD stage 3-4 with HK	Peritoneal dialysis	0.530	HSUV	Lee et al. 2005 ⁷⁶	Overall: N=416; PD: n=74. Mean age: 58.2 for males and 55.5 for females		Company changed source to Jesky et al. 2016: HSUV of 0.730 for end-stage renal disease. No comments from Committee
		Haemodialysis	0.443	HSUV	Lee et al. 2005 ⁷⁶	Overall: N=416; HD: n=99. Mean age: 58.2 for males and 55.5 for females		

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
		Transplant	0.712	HSUV	Lee et al. 2005 ⁷⁶	Overall: N=416; Transplant: n=209. Mean age: 58.2 for males and 55.5 for females		
TA481 (MTA) (2017) ⁸⁹	Adult kidney transplant recipients	Haemodialysis	0.277	Utility decrement	Liem et al. 2008 ⁷⁷	Meta-analysis; Mean age across studies (for HD): 60.4		Committee considered alternative approaches to modelling utilities, but considered this approach the most informative
		Peritoneal dialysis	0.264	Utility decrement	Liem et al. 2008 ⁷⁷	Meta-analysis; Mean age across studies (for PD): 57.9		
		Transplanted	0.053	Utility decrement	Liem et al. 2008 ⁷⁷	Meta-analysis; Mean age across studies (for transplant): 51.4		
TA358 (2015) ²⁶	Adults with autosomal dominant polycystic kidney disease (ADPKD)	Hospital or satellite haemodialysis	0.352	Disutility	Lee et al. 2005 ⁷⁶	Overall: N=416; HD: n=99. Mean age: 58.2 for males and 55.5 for females		–
		Home haemodialysis	0.352	Disutility	Lee et al. 2005 ⁷⁶	Overall: N=416; HD: n=99. Mean age: 58.2 for males and 55.5 for females		
		Peritoneal dialysis	0.262	Disutility	Lee et al. 2005 ⁷⁶	Overall: N=416;		

TA (year)	Population	Health state	Utility value	Utility value type	Source of utility data	Study characteristics for source of utility data	Further details	Committee preference
						PD: n=74. Mean age: 58.2 for males and 55.5 for females		
		Transplant year 1	0.148	Disutility	Clinical opinion	Not applicable		
		Transplant year 2+	0.082	Disutility	Lee et al. 2005 ⁷⁶	Overall: N=416; Transplant: n=209. Mean age: 58.2 for males and 55.5 for females		
		Disutility associated with haemodialysis complications	0.060	Disutility	NICE CG125	Not applicable		EAG preferred disutility of 0.020. Accepted by company. No comments from Committee
		Disutility associated with peritoneal dialysis complications	0.060	Disutility	NICE CG125	Not applicable		

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody-associated vasculitis; ADPKD, autosomal dominant polycystic kidney disease; CG, Clinical Guideline; CKD, chronic kidney disease; EAG, External Assessment Group; HD, haemodialysis; HK, hyperkalaemia; HSUV, health state utility value; IgAN, immunoglobulin A nephropathy; KRT, kidney replacement therapy; MTA, multi-technology appraisal; NG, NICE Guideline; NICE, National Institute for Health and Care Excellence; PD, peritoneal dialysis; SLR, systematic literature review; TA, technology appraisal; UPCR, urine protein to creatinine ratio.

Sources: Liem et al. 2008;⁷⁷ Cooper et al. 2020;⁸¹ FIDELIO-CKD;⁸² Lee et al. 2005;⁷⁶ Peasgood et al. 2016;⁸⁴ Nagasawa et al. 2018;⁸⁸ Dapagliflozin for treating chronic kidney disease (TA775);²⁹ Patisiran for treating hyperkalaemia (TA623);⁶⁷ Tolvaptan for treating autosomal dominant polycystic kidney disease (TA358);²⁶ NICE Clinical Guideline (CG125).⁹⁰

- e) Please cross validate the utility values in the current company base-case with the utility values sourced in b), c) and d).

Utility values generated from APPEAR-C3G trial data or identified in the TLR of previous NICE TAs (see Appendix F of the CS) were reviewed with UK clinical and health economic experts with regards to their suitability for use in the economic model.⁵ For CKD stages 1–4, utility values based on EQ-5D-5L collected in patients with C3G in the APPEAR-C3G trial (baseline mean age 27.9 years) were preferred for the base-case analysis, utilising values estimated with the regression model pooling CKD stages 1 and 2.⁵ Jesky et al. 2016,⁶³ a UK study which collected EQ-5D-3L data from 745 patients with CKD of any aetiology and a median age of 64 years, was considered appropriate to inform the utility value for CKD stage 5 (pre-KRT), for which no data were available from APPEAR-C3G.⁵ A scenario analysis explored the impact of using utility values from Jesky et al. 2016 for CKD stages 1–5 (pre-KRT).⁶³ Utility values from the Adelphi DSP, as reported by Lafayette et al. 2024,⁶² were not deemed clinically plausible (see response to question B13 b)) and therefore not used in the analysis.

To inform dialysis and post-transplant utilities in the economic model, experts considered the values published by Lee et al. 2005,⁷⁶ which were used in 7 previous NICE appraisals, as most appropriate.⁵ Lee et al. 2005, a UK study, estimated utility values for different KRT modalities from EQ-5D-3L collected in 416 patients (mean age 55.5 years in women, 58.2 years in men),⁷⁶ using a UK tariff;⁹¹ utility values for haemodialysis (HD), peritoneal dialysis (PD), and post-transplant were reported as 0.44, 0.53, and 0.71, respectively.⁷⁶ For the dialysis utility in the economic model, a weighted average was calculated according to the proportion of patients receiving each type of dialysis, sourced from a RaDaR analysis in patients with C3G (HD: 85.3%; PD: 14.7% [APD: 11.8%, CAPD: 2.9%]).¹²

Utility values from Liem et al. 2008⁷⁷ and Li et al. 2017⁹² were also discussed with clinical and health economics experts but not considered suitable for use in the model.⁵ The methodology of Liem et al. 2008⁷⁷ was considered to introduce uncertainty, since it is a meta-analysis of EQ-5D-based utility values reported across multiple international studies which did not consistently provide information on the value sets used; experts therefore preferred using Lee et al. 2005, given that it was a UK study.⁵ In addition, the small difference in the utility values of HD (0.56) and PD (0.58) reported by Liem et al. 2008⁷⁷ may underestimate the negative HRQoL impact of 3x weekly in-centre HD compared to at-home PD.⁵

Utility values from Li et al. 2017⁹² were not considered suitable for use in the economic model by the experts for several reasons.⁵ The publication reported a utility value for people on the transplant waiting list (0.77), rather than people on dialysis, and the clinical expert highlighted that people on the transplant waiting list tend to be healthier than people on long-term dialysis.⁵ This value was therefore not seen as representative of the HRQoL of people receiving chronic dialysis. Furthermore, the study used the preliminary value set for England to generate utility values from EQ-5D-5L,⁹³ which NICE advises against utilising.⁹⁴ Therefore, based on expert advice,⁵ utility values from Li et al. 2017 were not used in the analysis.

- f) Based on the cross-validation assessment, please provide an updated economic model and scenario analyses exploring utility values sourced in b), c) and d).

As described in the response to question B13 e), the utilities used within the model were selected following a TLR to gather potentially relevant sources from similar appraisals and discussions

with UK clinical experts, to ensure the utilities selected were relevant for C3G. No other utility values were considered appropriate for inclusion in the model. Results of the scenario analysis requested by the EAG (Liem et al. 2008 utility value for post-transplant health state) have been provided in the response to question B13 a).

B 14. The CS included SAE disutilities when related to iptacopan.

- a) Please provide evidence on the safety profile for the chosen comparators, and address whether safety profiles might differ when the comparator treatments are given respectively when iptacopan is added, implying an inclusion of comparator adverse events.

SoC is associated with various side effects, as discussed in Section 1.3.5 of the CS. Immunosuppressants including corticosteroids (CS) and mycophenolate mofetil (MMF) are associated with gastrointestinal side effects and increased risk of infections.^{50, 95} CS are also associated with various other side effects including musculoskeletal effects (osteoporosis and myopathy), weight gain, hypertension and insomnia which can be worsened by increased doses and continued administration.⁹⁶ Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin-receptor blockers (ARBs) were generally considered to have a favourable safety profile by UK clinicians participating in an advisory board.⁵⁰

In the APPEAR-C3G trial, iptacopan was administered in addition to optimised background therapy, including ACEis/ARBs at a maximally tolerated dose, with some patients also on concomitant CS and/or mycophenolic acids (MPA [including MMF]) or SLGT2is (continuation of stable dose during the trial).⁹⁷ Therefore, the safety data from the trial appropriately reflect the safety profile of iptacopan being administered in addition to SoC.

Furthermore, by not modelling AEs in the SoC arm of the economic model, while SAEs suspected to be related to iptacopan are modelled in the iptacopan arm, the economic model adopts a conservative approach, as all AE-related impacts are attributed to iptacopan rather than SoC.

- b) This approach resulted in infections being included with a disutility of 0.156, derived as the EQ-5D-3L score difference between acute presentation in cough and lower respiratory tract infections and recovery in week 4. Please report additional literature to verify this estimate for the UK setting.

The disutility was taken from a study by Oppong et al. 2013,⁹⁸ which was identified through a published SLR on the impact of acute pneumococcal disease on health state utility values.⁹⁹ Oppong et al. 2013 collected EQ-5D-3L from patients in England with cough and lower respiratory tract infections with a longitudinal study design. As Oppong et al. 2013 collected data in England and generated utility values using a UK tariff, it is therefore an accurate source for the UK setting. Utility values at acute presentation (baseline) and following recovery (Week 4) were presented,⁹⁸ allowing for the calculation of a disutility that was independent of the included population's general utility, and was therefore less impacted by differences in population characteristics such as age and comorbidities. On that basis, Oppong et al. 2013 is considered an appropriate source for the disutility and given the minimal impact of the AE disutility on the ICER, no additional literature has been searched for.

- c) Please provide an updated economic model and scenario analyses exploring alternative disutility values sourced in b).

In line with the response above to clarification question B14 b), the AE disutility used in the economic model was deemed suitable and therefore no additional values from the literature have been provided.

The disutility value of 0.156 from Oppong et al. was varied by 20% of the mean within the DSA and was not among the 10 most influential parameters within the economic model.

To test the impact of alternative disutility values further, two scenario analyses were run using disutility values of 0.1 and 0.2, respectively. Results are shown in Table 35 below, further confirming a minimal impact of the AE disutility on the ICER (range of [REDACTED] to [REDACTED] impact on the ICER across both scenarios).

Table 35: Scenario analysis results: Alternative AE disutilities

Disutility	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			% change in ICER (versus revised base case)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	
Revised company base case (AE disutility of 0.156)	██████	16.88	£355,162	15.13	██████	1.74	██████	█
Scenario analysis 1: AE disutility value of 0.1	██████	16.88	£355,162	15.13	██████	1.74	██████	████
Scenario analysis 2: AE disutility value of 0.2	██████	16.87	£355,162	15.13	██████	1.74	██████	████

Abbreviations: AE, adverse event; ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life year; SoC: Standard of Care.

Cost and healthcare resource use identification, measurement and valuation

B 15. Priority question. Table 45 of the CS presents acquisition costs for iptacopan with a cost per day and per year derived from the cost per pack. This approach implicitly assumes that a daily dosage can be acquired. Please provide an updated economic model and scenario analysis taking a per-pack costing approach rather than utilising acquisition costs per day to derive annual costs.

Within the economic model, the iptacopan price per year is calculated via a daily iptacopan price (for dosing 200 mg twice daily). This is then divided by the number of cycles per year and applied to the number of patients on iptacopan per cycle throughout the time horizon to calculate the total acquisition cost of iptacopan.

We agree that this approach implies that individual iptacopan capsules can be acquired and therefore neglects to account for the cost of pack wastage when a patient discontinues iptacopan. In the economic model submitted with the clarification questions response, the approach to calculating the acquisition cost of iptacopan has been adjusted to account for wastage, as described below.

With each pack containing 56 capsules of iptacopan 200 mg and twice daily dosing, approximately 3.26 packs are required per 3-month model cycle. Therefore, the maximum number of iptacopan packs that a patient opens per model cycle is 4. To conservatively reflect the maximum wastage possible when a patient discontinues iptacopan, the cost of an additional ~0.74 packs is added to the total acquisition cost of iptacopan, thereby accounting for the cost of 4 packs in a patient's final model cycle on iptacopan. This change in costing has been implemented in cell EK2 of the 'Iptacopan' tab in the economic model.

The cost of iptacopan pack wastage has been incorporated in a revised company base case, which is presented in Table 36 below; the impact on cost-effectiveness results is small (change in ICER from the original company base case is [REDACTED]).

Table 36: Revised company base case accounting for the cost of iptacopan wastage

Scenario	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			% change in ICER versus original company submission
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	
Original company submission base case	██████	16.88	£355,162	15.13	██████	1.74	██████	█
Revised company base case accounting for wastage at iptacopan discontinuation	██████	16.88	£355,162	15.13	██████	1.74	██████	██████

Abbreviations: ICER: incremental cost-effectiveness ratio, n/a: not applicable; QALY: quality adjusted life year; SoC: Standard of Care.

B 16. Table 50 of the CS presents the (post-)transplant and dialysis costs. For reproducibility by the EAG, please provide a clear and detailed overview of the each calculation including individual parameter inputs and corresponding sources.

Details of the inputs used and corresponding sources to derive the costs seen within Table 50 of the CS are summarised in Table 37–Table 42 below. In the economic model, the derivation of these costs can be found within cells D41:D47 of the ‘Cost data’ tab.

The approach to calculating transplant costs is in line with the approach used in NICE TA775 (details were provided in the response to clarification question B22 in TA775).²⁹ This same approach was subsequently used in NICE TA942²⁷.

Table 37: Derivation of per-event transplant cost (one-off cost per transplantation)

Currency Code	Activity	Unit cost	Total cost	Source
LA01A - Kidney Transplant, 19 years and over, from Cadaver Non-Heart-Beating Donor	855	£21,418	£18,312,571	Unit costs and activities are sourced from the National Schedule of NHS Reference Costs 2023/24. ³⁶
LA02A - Kidney Transplant, 19 years and over, from Cadaver Heart-Beating Donor	895	£18,467	£16,528,250	
LA03A - Kidney Transplant, 19 years and over, from Live Donor	574	£17,473	£10,029,590	
LA10Z - Live Kidney Donor Screening	1,178	£411	£483,622	
LA11Z - Kidney Pre-Transplantation Workup of Live Donor	1,975	£517	£1,020,102	
LA12A - Kidney Pre-Transplantation Workup of Recipient, 19 years and over	10,101	£531	£5,362,203	
LA13A - Examination for Post-Transplantation of Kidney of Recipient, 19 years and over	74,426	£320	£23,790,463	
LA14Z - Examination for Post-Transplantation of Kidney of Live Donor	2,773	£343	£951,669	
Living Donor Transplantation Costs				
Kidney transplantation cost, living donor (LA03A)	£17,473		Unit costs and activities are sourced from the National Schedule of NHS Reference Costs 2023/24. ³⁶	
Pre-transplantation cost - recipient (LA12A total cost distributed across all transplantation events going ahead [activity of currency codes LA01A:LA03A])	£2,307			
Pre-transplantation cost - live donor (LA10Z, LA11Z total cost	£2,620			

Currency Code	Activity	Unit cost	Total cost	Source
distributed across all live transplantation events going ahead [activity of currency code LA03])				
Post-transplantation examination cost - recipient (LA13A total cost distributed across all transplantation events going ahead [activity of currency codes LA01A:LA03A])	£10,237			
Post-transplantation examination cost – live donor (LA14Z total cost distributed across all live transplantation events going ahead [activity of currency code LA03])	£1,658			
Total cost per living donor transplantation = £17,473 + £2,307 + £2,620 + £10,237 + £1,658	£34,295			
Deceased Donor Transplantation Costs				
Kidney transplantation cost, deceased donor (weighted average LA01A, LA02A)	£19,909			Unit costs and activities are sourced from the National Schedule of NHS Reference Costs 2023/24. ³⁶
Pre-transplantation cost - recipient (LA12A total cost distributed across all transplantation events going ahead [activity of currency codes LA01A:LA03A])	£2,307			
Post-transplantation examination cost - recipient (LA13A total cost distributed across all transplantation events going ahead [activity of currency codes LA01A:LA03A]))	£10,237			
Total cost per deceased donor transplantation = £19,909 + £2,307 + £10,237	£32,453			
Weighted average of living (34.2%) and deceased (65.8%) donor transplantation costs	£33,083			Proportions receiving living and deceased donor transplants are taken from RaDaR data in patients with C3G. ¹²

Table 38: Derivation of annual post-transplant costs

Category	Calculation	Source
Post-transplant costs	$\text{£5,000} \times 1.493025252 / 1.032 = \text{£7,233.65}$	£5,000: Annual cost of immunosuppression, NHS Blood and Transplant 2009. ¹⁰⁰
		1.493025252: The cumulative inflation factor (excluding capital) for the 2022/23 fiscal year from the Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care, PSS Pay & Price Index, Table 12.1.2. ¹⁰¹
		1.032: The cumulative inflation factor (excluding capital) for the 2008/2009 fiscal year from the Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care, PSS Pay & Price Index, Table 12.1.2. ¹⁰¹

Abbreviations: PSS: Personal and Social Services.

Table 39: Derivation of annual CAPD costs

Currency code	Activity	Total Cost
LD11A - Continuous Ambulatory Peritoneal Dialysis, 19 years and over	328,259	£31,534,604
Average unit cost	£96.07	
CAPD takes place daily, therefore multiplied by number of days in a year (365.25)^{34, 35}	£35,088.19	

Abbreviations: CAPD: continuous ambulatory peritoneal dialysis.

Footnote: Costs and activities sourced from the National Schedule of NHS Reference Costs 2023/24.³⁶

Table 40: Derivation of annual APD costs

Currency code	Activity	Total Cost
LD12A - Automated Peritoneal Dialysis, 19 years and over	439,001	£47,716,114
LD13A - Assisted Automated Peritoneal Dialysis, 19 years and over	97,650	£12,277,809
Weighted average	£111.79	
APD takes place daily, therefore multiplied by number of days in a year (365.25)^{34, 35}	£40,832.46	

Footnote: Costs and activities sourced from the National Schedule of NHS Reference Costs 2023/24.³⁶

Abbreviations: APD: automated peritoneal dialysis.

Table 41: Derivation of annual HD costs

Currency code	Activity	Total Cost
LD01A - Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	533,099	£113,553,034
LD02A - Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	593,114	£132,057,133
LD03A - Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	15,741	£3,366,574
LD04A - Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	12,815	£3,069,878
LD05A - Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	727,701	£145,217,929

LD06A - Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	1,053,946	£216,248,228
LD07A - Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	19,350	£4,059,297
LD08A - Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	24,537	£5,143,118
LD09A - Home Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	28,628	£9,193,368
LD10A - Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	70,673	£18,750,490
Weighted average	£211.28	
HD takes place three times a week, therefore multiplied the weighted average by $365.25/(7*3)$ ^{34, 35}	£33,072.88	

Footnote: Costs and activities sourced from the National Schedule of NHS Reference Costs 2023/24.³⁶

Abbreviations: HD: haemodialysis.

Table 42: Derivation of annual HD transportation costs

Description	Value	Source
Unit cost of transport per in-centre HD session	$£46 * 1.493025252 / 1.0831872 = £63.40$	Liu et al. 2015. ¹⁰² Reported value for transport cost per in-centre HD session of £46 (based on the National Kidney Care Audit, Patient Transport Survey from 2010) inflated from 2010/2011 fiscal year to 2022/23 using the PSS Pay & Price Index. ¹⁰¹ 1.493025252 and 1.0831872: The cumulative inflation factor (excluding capital) for the 2022/23 and 2010/2011 fiscal year respectively from the Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care, PSS Pay & Price Index, Table 12.1.2. ¹⁰¹
HD sessions and therefore transport costs occur three times a week	$£63.40 * 365.25 / (7 * 3) = £9,925.10$	N/A
Apply proportion of patients that receive in-centre HD among all patients receiving HD	$£9,925.10 * (1 - 99301/3079604) = £9,605.07$	Proportion receiving in centre HD: 1 minus the sum of currency codes LD09A and LD10A divided by sum of all patients receiving HD (sum of activity for currency codes LD01A:LD10A) Table 41. Costs derived as per Table 41, National Schedule of NHS Reference Costs 2023/24 ³⁶

Abbreviations: HD: haemodialysis; n/a: not applicable; NHS: National Health Service; PSS: Personal Social Services.

A total dialysis cost of £42,237.61 was calculated by taking a weighted average across dialysis modalities, and subsequently adding the cost of transport applied to the patients receiving HD. Proportions receiving each dialysis modality were based on a RaDaR analysis in patients with C3G.¹² The mathematical calculation is as follows:

$$£42,237.61 = £35,088.19 * 2.9\% + £40,832.46 * 11.8\% + £33,072.88 * 85.3\% + £9,605.07 * 85.3\%$$

B 17. SAEs suspected of being related to iptacopan were included in the model. Table 52 of the CS provides a weighted average unit cost, weighted by total activity of respective HRG codes in the NHS reference costs. The EAG was unable to reproduce the weighted average cost of £2,819.03.

- a) Please provide a detailed overview of how this weighted average unit cost was derived using the NHS National Cost Collection 2023/24 with reference to the variable headings utilised.

Information on currency codes, total unit costs and activity in the National Schedule of NHS Reference Costs which were used to calculate the weighted average unit cost of £2,819.03 can be found below in Table 43.

Table 43: Total costs across all events used to calculate the cost of adverse events

National Schedule of NHS Reference Costs 2023/24 Tab ³⁶	National Schedule of NHS Reference Costs 2023/24 Department Currency ³⁶	Total Unit Cost	Activity
Summary: HRG Cost	DZ11K - Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 14+	£8,631.15	5,326
	DZ11L - Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 9-13	£7,031.82	3,236
	DZ11M - Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 0-8	£4,412.43	1,167
	DZ11N - Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 13+	£6,050.30	15,384
	DZ11P - Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12	£4,287.51	11,151
	DZ11Q - Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-7	£3,256.55	5,012
	DZ11R - Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 14+	£3,792.76	103,946
	DZ11S - Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10-13	£2,644.57	138,222
	DZ11T - Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9	£1,965.21	100,966
	DZ11U - Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-6	£1,581.91	83,178
	DZ11V - Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3	£1,084.53	71,531

National Schedule of NHS Reference Costs 2023/24 Tab ³⁶	National Schedule of NHS Reference Costs 2023/24 Department Currency ³⁶	Total Unit Cost	Activity
	DZ23H - Bronchopneumonia with Multiple Interventions	£9,086.57	264
	DZ23J - Bronchopneumonia with Single Intervention, with CC Score 11+	£5,731.76	614
	DZ23K - Bronchopneumonia with Single Intervention, with CC Score 0-10	£4,088.68	256
	DZ23L - Bronchopneumonia without Interventions, with CC Score 11+	£3,356.60	5,454
	DZ23M - Bronchopneumonia without Interventions, with CC Score 6-10	£2,067.96	3,499
	DZ23N - Bronchopneumonia without Interventions, with CC Score 0-5	£1,323.40	2,243
	WJ06A - Sepsis with Multiple Interventions, with CC Score 9+	£10,656.55	4,549
	WJ06B - Sepsis with Multiple Interventions, with CC Score 5-8	£9,428.28	2,732
	WJ06C - Sepsis with Multiple Interventions, with CC Score 0-4	£7,373.84	819
	WJ06D - Sepsis with Single Intervention, with CC Score 9+	£7,176.28	7,454
	WJ06E - Sepsis with Single Intervention, with CC Score 5-8	£6,064.01	6,899
	WJ06F - Sepsis with Single Intervention, with CC Score 0-4	£5,023.56	2,751
	WJ06G - Sepsis without Interventions, with CC Score 9+	£3,741.97	51,237
	WJ06H - Sepsis without Interventions, with CC Score 5-8	£2,790.26	82,647
	WJ06J - Sepsis without Interventions, with CC Score 0-4	£2,032.47	54,219
Weighted average		£2,819.03	

Abbreviations: CC: complication or comorbidity; HRG: Healthcare Resource Group

- b) Please provide justification for the chosen approach, rather than deriving a unit cost from the National Mean for each given HRG Code.

The adopted approach is considered the most appropriate as it adjusts the costs associated with lobar, atypical or viral pneumonia (DZ11), bronchopneumonia (DZ23), and sepsis (WJ06) and their respective CC Scores based on their relative frequency as recorded in the NHS Reference Costs.³⁶ A simple average of the costs of grouped HRG codes DZ11, DZ23 and WJ06 would assume that these occur at equal frequency, which would be incorrect.

- c) Please provide a scenario analysis utilising an average unit cost derived from the national means for the HRG codes presented in CS Table 52.

As requested by the EAG, a scenario analysis has been conducted calculating the weighted average of each grouped HRG code (across all CC scores) and subsequently taking a simple average of these:

SAE scenario cost = (Weighted average across code DZ11 + Weighted average across code DZ23 + Weighted average across code WJ06) / 3

This results in an average cost of £2,951.90. A scenario analysis shows limited impact on the cost-effectiveness results (see Table 44). However, as explained in the response to b), the SAE cost as used in the CS is considered more appropriate.

Table 44: Scenario analysis results: Alternative SAE cost

Scenario	Iptacopan + SoC		SoC		Iptacopan + SoC vs SoC			% change in ICER (versus revised base case)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	
Revised company base case (SAE cost = £2,819.03)	██████	16.88	£355,162	15.13	██████	1.74	██████	█
Scenario analysis with alternative SAE cost (£2,951.90)	██████	16.88	£355,162	15.13	██████	1.74	██████	██████

Abbreviations: ICER: Incremental cost-effectiveness ratio; QALY: quality adjusted life year; SAE: serious adverse event; SoC: standard of care

B 18. The CS states that all costs were inflated to the 2022/2023 fiscal year. Please clarify why 2022/23 was selected, rather than 2023/2024. Further, please specify how costs derived from NHS National Cost Collection 2023/24 were handled and where inflation calculation can be found in the economic model.

Costs were inflated to the 2022/23 fiscal year as relevant, using the NHSCII Pay and Price Index.¹⁰¹ At the time of the company submission, the latest PSSRU Unit Cost of Health and Social Care Manual was the 2023 edition, which did not include inflation indices up to the 2023/24 fiscal year. This created a small misalignment in cost year between the inflated costs and costs informed by the National Schedule of NHS Costs 2023/24, but in all cases used the most recent available information.³⁶

In the economic model, inflation calculations can be found within each inputs cell calculation where applicable (e.g., cell D47 within the 'Cost data' tab for the inflation of costs sourced from Liu et al. 2015).¹⁰² Each inflation calculation references cells R13:R27 of the 'Cell links' tab which shows the cumulative inflation factor sourced from the PSSRU Unit Cost of Health and Social Care Manual 2023.¹⁰¹

Results

B 19. Tables 1, 2 and 3 of Appendix H in the CS present disaggregated costs, outcomes, and kidney survival outcomes, respectively.

- a) In Table 1, dialysis and (post-)transplant costs are significantly higher for the SoC arm versus the iptacopan +SoC arm. Please justify and discuss the plausibility of the presented results.

The available clinical trial data on eGFR stabilisation with iptacopan treatment, as summarised in Section 2 of the CS, suggest that iptacopan is able to slow the progression of C3G in a meaningful way.^{4, 10} By slowing the progression of C3G, iptacopan is expected to maintain patients in earlier CKD stages for longer, and thus prolong kidney survival and delay the need for KRT. For example, in the economic model base case, kidney survival at 10 years is estimated as 90.22% for the iptacopan arm compared with 51.84% for the SoC arm. Fewer patients in the iptacopan arm experiencing kidney failure and requiring KRT early in the disease course results in a reduction of dialysis and transplant costs compared with the SoC arm.

Dialysis and transplant are the health states associated with the highest healthcare resource utilisation in chronic kidney diseases.¹⁰³ A reduction in the need for dialysis or transplants is meaningful not only in terms of direct NHS cost, but also beneficial from an NHS capacity perspective and leads to important improvements for patients, given the risks and quality of life impacts of dialysis and transplantation.

- b) Table 2 shows that total QALYs in CKD stage 1 for the iptacopan +SoC arm are 110.06% higher than in the SoC arm with the % absolute QALY increments falling in

later stages. Please justify and discuss the plausibility of the results presented in table 2.

As noted in response to question B19 a), the available clinical trial data suggest that iptacopan is able to slow C3G progression, thereby maintaining patients in earlier CKD stages for longer, while reducing the number of patients reaching kidney failure, compared to SoC alone. By slowing progression, patients receiving iptacopan stay in earlier CKD stages for longer and therefore accrue more QALYs in early CKD stages than patients in the SoC arm, who progress to kidney failure more quickly and consequently accrue more QALYs in the dialysis and transplant health states.

- c) Table 3 presents kidney survival at 5 years, 10 years, as well as the median time to kidney failure (years). Please expand table 3 to include time points at 1, 2, 3, 4, 5, 10, 15, and 20 years, and to capture the time to each CKD stage.

An updated table showing kidney survival for additional time points is provided in Table 45, and time to each CKD stage is shown in Table 46. Please note that time to next state for the iptacopan + SoC arm has not been provided, given that the iptacopan arm in the model consists of patients on iptacopan and patients who have discontinued iptacopan and switched to SoC alone, with proportions varying over the model time horizon; time to next state therefore cannot be easily calculated.

Table 45. Kidney survival outcomes

	SoC	Iptacopan + SoC
Kidney survival at 1 years	97.80%	99.82%
Kidney survival at 2 years	94.65%	99.52%
Kidney survival at 3 years	90.86%	99.07%
Kidney survival at 4 years	86.45%	98.45%
Kidney survival at 5 years	81.45%	97.65%
Kidney survival at 10 years	51.84%	90.22%
Kidney survival at 15 years	27.03%	75.84%
Kidney survival at 20 years	12.56%	55.25%
Median time to kidney failure (years)	10.25	21.00

Abbreviations: SoC, standard of care.

Table 46. Time to next state (years)

	SoC
CKD stage 1 → CKD stage 2	5.8
CKD stage 2 → CKD stage 3a	3.1
CKD stage 3a → CKD stage 3b	2.1
CKD stage 3b → CKD stage 4	2.1
CKD stage 4 → CKD stage 5 (pre-KRT)	1.6
CKD stage 5 (pre-KRT) → KRT	0.5

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; SoC, standard of care.

B 20. For the lifetime time horizon, please provide an overview of the total costs and QALYs gained in the observed period versus the extrapolated period. Please provide this for the iptacopan + SoC and the SoC arm separately and comment on the plausibility of the presented results.

Table 47 below shows results for the total costs and QALYs accrued across the observed period and the extrapolated period for SoC and iptacopan + SoC, respectively.

The observed period for SoC was taken as 2.5 years in line with the maximum duration of pre-iptacopan data informing the eGFR slope for SoC. The observed period for iptacopan + SoC was taken as 2 years in line with the maximum duration of on-iptacopan data informing the eGFR slope for iptacopan (APPEAR-C3G + extension study data in the base-case analysis).

Table 47: Total costs and QALYs for the observed period versus the extrapolated period

Period	SoC		Iptacopan + SoC	
	Total Costs	Total QALYs	Total Costs	Total QALYs
Observed period (SoC: 2.5 years, iptacopan + SoC: 2 years)	£3,341	2.12	██████	1.73
Extrapolated period	£351,821	13.01	██████	15.15

Abbreviations: QALY: quality adjusted life year; SoC, standard of care.

Footnote: Results based on the revised company base case.

Sensitivity/scenario analyses

B 21. Priority question. When running the PSA, the EAG noticed that this has implications on the deterministic results in the model (including errors and implausible cost results). In addition, the PSA does not vary trial HSUVs, the proportion of CAPD/APD/HD patients, resource use parameters, and eGFR midpoint values.

- a) Please provide an updated economic model with this implication fixed and include an overview of all changes made within the economic model.

Novartis has not observed any implications on the deterministic results or other unintended consequences when running the PSA.

It is possible that what the EAG has observed occurs if a user changes a model input and subsequently runs the PSA without making further necessary changes on the 'Control' tab. If edits are being made to the model prior to running the PSA, it is necessary to run the 'CopyFormulas' macro by pressing the button in cell C2 of the 'Control' tab.

- b) For PSA reproducibility, please ensure that a fixed seed is included.

A fixed seed has now been included within the economic model and within the updated PSA results presented below in response to question B21 d). This can be found in cell C49 of the 'Settings' tab.

- c) Please provide justification for the decisions to exclude these parameters from the PSA.

Trial health state utility values (HSUVs) are already varied within the PSA in the originally submitted economic model. Trial HSUVs, found within cells E15:E19 of the 'Utility data' tab, are derived from the coefficients of a linear regression model. The parameters from the regression model are varied within the PSA using a Cholesky decomposition distribution, which can be found in rows 570:574 of the 'Control' tab. Details of the variance-covariance matrix used within the Cholesky decomposition can be seen in cells BE21:BQ26 on the 'Control' tab. Please note that the parameters within rows 22:26 of the 'Control' tab need not be varied given the individual components are varied within rows 570:574.

The economic model submitted with the clarification questions response has been updated to vary the proportion of CAPD/APD/HD patients (rows 42:44, 'Control' tab) and the proportion receiving each healthcare resource use (rows 108:234, 'Control' tab) in the PSA.

eGFR midpoint values are not varied within the PSA, as they are part of the model structure and represent structural uncertainty rather than an input associated with parameter uncertainty. If these values were to be varied within the PSA, variable progression through CKD stages would be modelled i.e., each probabilistic run would result in a different midpoint for each CKD stage which in turn would cause progression throughout the modelled health states to be based on inconsistent distances between CKD stages (in other words, progression would no longer be uniform). Therefore, eGFR midpoint values have not been included within the PSA.

Novartis acknowledges that using the midpoint of each CKD stage (midpoint between upper and lower bound defining the CKD stage) for CKD stage transitions is a simplification, but one that was considered necessary in a Markov cohort approach. A scenario was provided in the CS where transition probabilities are calculated based on the difference between the upper bounds of CKD stages rather than midpoints, with a limited change (+█%; see Table 51) compared to the base case ICER.

- d) Please provide an updated economic model and results for the PSA that includes the aforementioned parameters: trial HSUVs, proportions of CAPD/APD/HD patients, resource use parameters, and eGFR midpoint values.

In line with the responses above, an updated economic model has been provided which additionally varies the proportions of CAPD/APD/HD patients and resource use parameters. Whilst updating these parameter inclusions within the PSA, the model has also been amended to additionally vary the KRT threshold, maximum age for transplant, and vaccination and antibiotic annual frequencies and proportion of patients within the PSA in the updated economic model.

Please note that when adding inputs to the PSA which correspond to proportions equal to 100% e.g., the proportion receiving antibiotics, a beta distribution is used. For a beta distribution to

sample values between 0 and 1 correctly, the mean value used within the formula to calculate the beta distribution cannot be a value of 1 (which would correspond to the modelled base case value of 100%). As a result, a simplification has been made to use a mean value of 99% (0.99) within the beta distribution instead of the modelled base case value of 100%. Within the economic model this is applied to the proportion receiving each resource use (rows 108:114, 124:130, 140:146, 156:162, 172:178, 188:194, 204:210, 220:226, 494, 497, 499 and 502 of the 'Control' tab).

Updated probabilistic results (using 1,000 simulations) are presented in Table 48 and Table 49. An updated probabilistic ICER convergence plot, cost-effectiveness scatter plot and cost-effectiveness acceptability curve are shown in Figure 15, Figure 16 and Figure 17.

Table 48: Revised probabilistic base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
SoC	£355,352	21.12	15.15	-	-	-	-
Iptacopan + SoC	██████	21.56	16.69	██████	0.44	1.54	██████

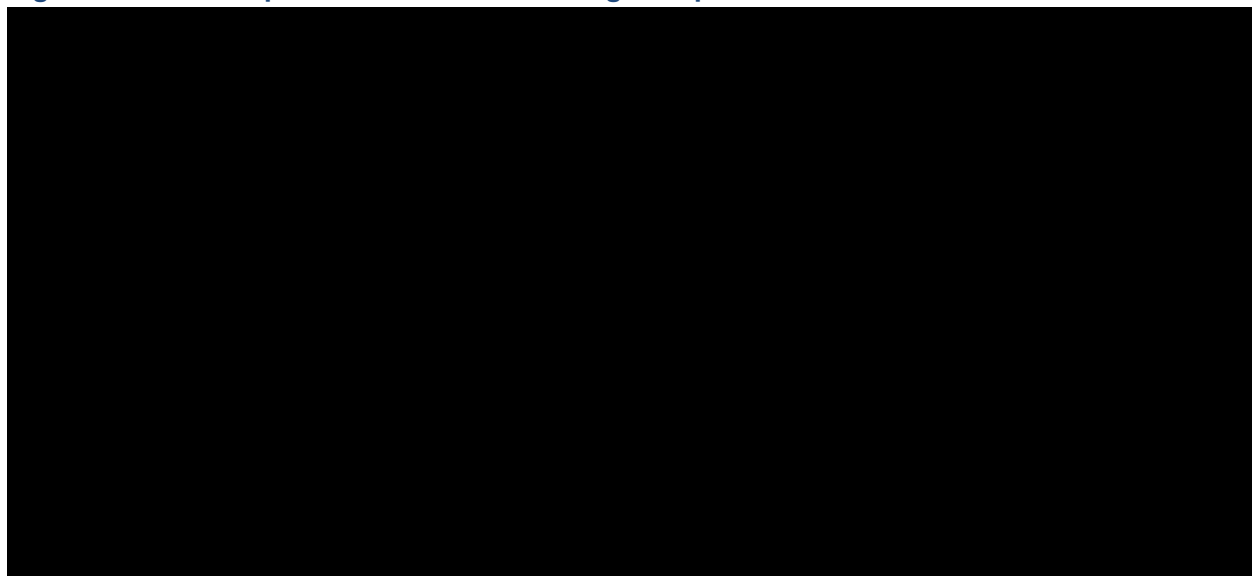
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality adjusted life year; SoC, standard of care.

Table 49: Revised probabilistic net health benefit results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
SoC	£355,352	15.15	-	-	-	-
Iptacopan + SoC	██████	16.69	██████	1.54	- █████	- █████

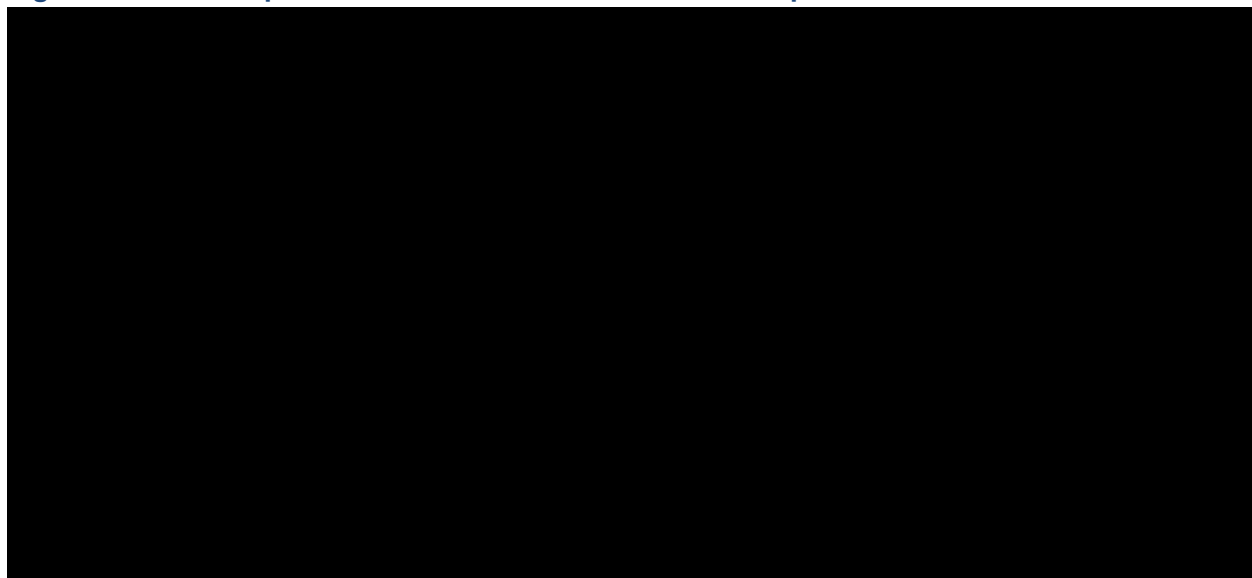
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NHB: net health benefit; QALY: quality adjusted life year; SoC, standard of care.

Figure 15: Revised probabilistic ICER convergence plot



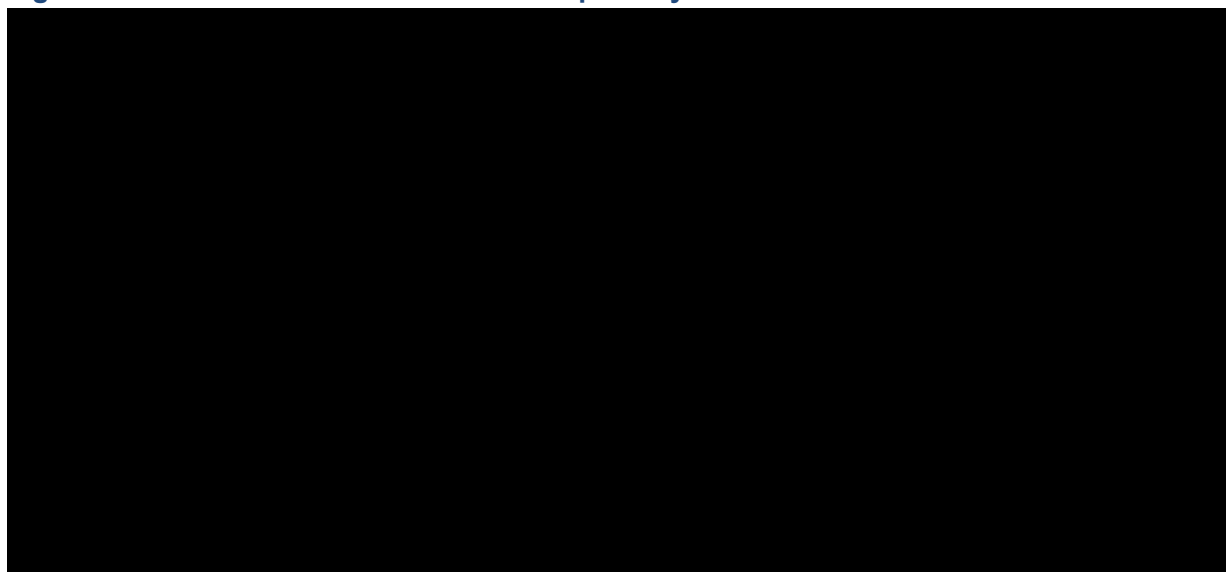
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC, standard of care.

Figure 16: Revised probabilistic cost-effectiveness scatter plot



Abbreviations: QALY: quality-adjusted life year.

Figure 17: Revised cost-effectiveness acceptability curve from base-case PSA



Abbreviations: PSA: probabilistic sensitivity analysis; SoC: standard of care

B 22. Priority question. The EAG encountered an error when attempting to run the deterministic sensitivity analysis (DSA). “Microsoft Visual Error Basis Run-time error ‘13’: Type mismatch” was displayed when trying to run the DSA. Further, Appendix L provides a summary of variables included in the DSA, however, it is unclear from this table which variables are excluded from the DSA.

- a) Please provide an updated economic model having addressed this DSA functionality issue and describe all adjustments made to the submitted economic model.

Novartis has not observed the described error and has reconfirmed that the DSA operates correctly in the economic model submitted to NICE. The "Microsoft Visual Error Basis Run-time error ‘13’: Type mismatch" might occur if the file path is too long or if changes have been made to the model base case which the model is then incompatible with.

- b) Please specify which parameters were not included in the DSA and provide justification for each excluded parameter.

Table 50 presents parameters excluded from the DSA in the originally submitted economic model and the associated justification. In addition to those in Table 50, placeholder inputs or those not included in the company base case are not varied in the DSA (e.g., placeholder adverse event inputs or cardiovascular event disutilities) as these do not affect the base case model results and would slow down run time.

Please note that within the DSA, similarly to the approach within the PSA, trial health state utility values are based on a linear coefficient regression model. These coefficients are varied within the DSA in rows 570:574 of the ‘Control’ tab, therefore rows 22:26 of the ‘Control’ tab are not required to be varied within the DSA.

Please also note that the percentages of patients receiving CAPD/APD/HD (rows 42:44, 'Control' tab) as well as the initial health state distributions (rows 436:458, 'Control' tab) were erroneously varied in the DSA of the original economic model, however these are not varied within the updated economic model. The reason is that both the proportion of patients receiving the various types of dialysis and the proportion of patients in each CKD stage at baseline (when entering the economic model) must sum to 100%, which cannot be achieved when varying these inputs independently within the DSA.

Table 50: Parameters excluded from the DSA in the originally submitted economic model and the associated justification

Parameter	Justification	Varied in updated model?
Time horizon	The time horizon is a fundamental model assumption and is set to a lifetime horizon (up to age 100), in accordance with the NICE reference case. ²⁵ Please note that the baseline age is varied within the DSA, with the time horizon automatically adjusting to a value corresponding to age 100.	No
eGFR lower bounds for CKD stages 1–4	These bounds are defined criteria for CKD staging forming part of the model structure, with no associated parameter uncertainty.	No
Deceased donor transplant % patients	The percentage of deceased donor transplants is set to 1 minus the percentage of living donor transplants. The percentage of living donor transplants is varied within the DSA, and therefore the percentage of deceased donor transplants is varied indirectly owing to the fact that the total percentage must add to 100%.	No
Treatment dose, drug strength, units per pack, dose intensity, and dose per day	These inputs are indirectly varied by varying the overall treatment acquisition costs, which is deemed sufficient to capture their impact on model outcomes.	No
Iptacopan price	The iptacopan price is not associated with uncertainty and therefore it was not included in the DSA.	No
Administration cost, oral	The cost of oral administration is set to £0 therefore does not require any variation.	No
Health state monitoring resource usage frequencies	The health state monitoring resource use unit costs and the proportion of patients using the resource were varied in the DSA, but the annual resource use frequencies were not. All health state monitoring resource use proportions, frequencies and costs are now varied within the DSA of the updated economic model. Please note that the proportion receiving each resource use is capped at a maximum value of 100%. Health state monitoring resource use frequencies, proportions and costs are not a key model driver.	Yes
Cost of death	The model has been updated to include variation of the cost of death in the DSA; it has not been identified as a key model driver.	Yes
Allograft failure post-transplant (HR iptacopan vs SoC)	As the model assumes patients discontinue iptacopan at the start of KRT, no treatment effect is applied, making the hazard ratio fixed at 1 by assumption.	No

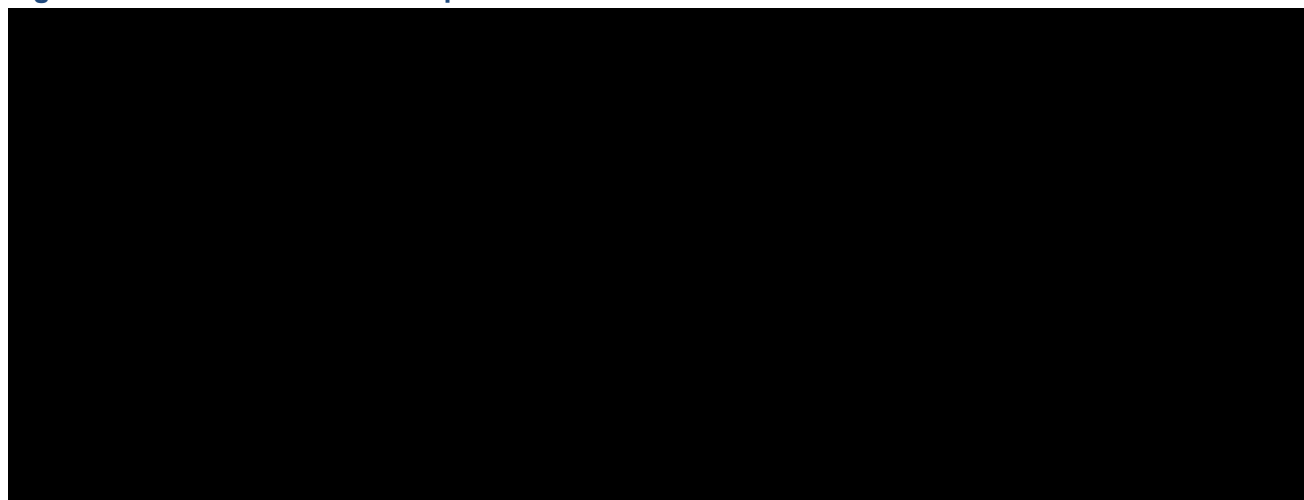
Parameter	Justification	Varied in updated model?
KRT eGFR threshold	The model has been updated to include variation of the KRT eGFR threshold in the DSA; it has not been identified as a key model driver.	Yes
Maximum age for transplant	The model has been updated to include variation of the maximum age for transplant in the DSA; it has not been identified as a key model driver.	Yes
Vaccine and antibiotic proportion of patients and annual frequencies	The DSA within the original company submission varied vaccine and antibiotic costs only. Within the updated economic model, the proportion of patients receiving vaccines and antibiotics and the annual frequency are now varied; these have not been identified as a key model driver.	Yes
HR for CV events	CV events are not included within the model base case therefore do not need to be varied within the DSA.	No
eGFR midpoints	As discussed within the response to clarification question B21 c), eGFR midpoint values are considered as part of the structure of the model and therefore should not be varied independently.	No
Placeholder inputs, index values	All placeholder inputs or values used as indexes are not varied in the DSA given their lack of impact on results.	No

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; DSA, deterministic sensitivity analysis; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KRT, kidney replacement therapy; NICE, National Institute for Health and Care Excellence; SoC, standard of care.

- c) Please provide an updated economic model and results for the PSA that includes the aforementioned parameters: trial HSUVs, proportions of CAPD/APD/HD patients, resource use parameters, and eGFR midpoint values.

An updated economic model has been provided with the clarification questions response. Updated PSA results are presented in the response to question B21 d), while an updated DSA tornado plot using the revised model base case (accounting for wastage) and the revised DSA parameter inclusions as detailed above is presented in Figure 18. None of the newly added parameters to the DSA appear in the top 10 most influential parameters on the ICER. Please note that the percentage of patients receiving HD was within the tornado plot of the original company submission, whereas this does not appear in Figure 18 given its exclusion from the DSA within the updated economic model, as explained in the response to question B22 b).

Figure 18: Revised DSA tornado plot



Abbreviations: DSA: deterministic sensitivity analysis; eGFR, estimated glomerular filtration rate; HSUV, health-state utility value; ICER, incremental cost-effectiveness ratio; SoC, standard of care.

In addition to the updates to the PSA and DSA, the model base case has been revised to account for pack wastage of iptacopan at discontinuation. As such, the deterministic scenario analyses of the original company submission are presented below in Table 51 also incorporating this change.

As in the original company submission, the scenario analysis with the greatest impact on the base-case ICER is scenario #3, utilising eGFR slope data from the 6-month placebo-controlled period of APPEAR-C3G, which increased the ICER by [REDACTED]. As mentioned within section 3.10.1 of original company submission, this result should be interpreted with caution since UK clinicians advised that predictions of SoC arm disease progression in this scenario lacked clinical validity (model-predicted median time to kidney failure with SoC 22.8 years, compared with approximately 10 years based on literature and advisors' clinical experience).^{4, 5} All other scenarios had a minor impact on the ICER.

Table 51: Revised deterministic scenario analysis results

#	Scenario analysis description	Base case description	Incremental costs	Incremental QALYs	ICER	% ICER change (versus revised base case)
-	Revised base case (deterministic)	-	[REDACTED]	1.74	[REDACTED]	[REDACTED]
Model settings						
1	CV events included	CV events not included	[REDACTED]	1.74	[REDACTED]	[REDACTED]
Model inputs						
2	eGFR slope data from pooled population (APPEAR-C3G)	eGFR slope data from APPEAR-C3G population (up	[REDACTED]	1.62	[REDACTED]	[REDACTED]

#	Scenario analysis description	Base case description	Incremental costs	Incremental QALYs	ICER	% ICER change (versus revised base case)
	and Phase 2 native kidney cohort; up to 4.7 years iptacopan treatment duration)	to 2 years iptacopan treatment duration)				
3 ^a	eGFR slope data from APPEAR-C3G placebo comparison (based on 6 months of data)	eGFR slope data from APPEAR-C3G population (up to 2 years iptacopan treatment duration)	████████	1.36	████████	████████
4	Baseline characteristics and initial health state distribution from RaDaR	Baseline characteristics and initial health state distribution from APPEAR-C3G	████████	1.66	████████	████████
5	CKD stage transitions at upper eGFR bound of CKD stage	CKD stage transitions at midpoint of CKD stage, except for transition to KRT at KRT threshold	████████	1.75	████████	████████
6	Transplant eligibility of 93.18% for initial and 73.18% for subsequent transplants	Transplant eligibility of 83.2% for initial and subsequent transplants	████████	1.73	████████	████████
7	No maximum age for transplant	Maximum age for receipt of transplant 80 years	████████	1.74	████████	████████
8	Discontinuation of iptacopan, SGLT2i, MMF, CS upon entering CKD stage 5 (eGFR≤15 mL/min/1.73m ²)	Discontinuation of iptacopan, SGLT2i, MMF, CS upon reaching KRT threshold (eGFR ≤7.6 mL/min/1.73m ²)	████████	1.72	████████	████████
9	Mortality HRs based on Go et al. 2004	Mortality SMRs based on Wong et al. 2024	████████	1.81	████████	████████

#	Scenario analysis description	Base case description	Incremental costs	Incremental QALYs	ICER	% ICER change (versus revised base case)
10	CKD stage 1–4 utility values from Jesky et al. 2016	CKD stage 1–4 utility values from APPEAR-C3G	██████	1.82	██████	██████
11	Proportion of patients receiving SGLT2i assumed as 50%	Proportion of patients receiving SGLT2i based on APPEAR-C3G (5.4%)	██████	1.74	██████	██████
12	Healthcare resource use based on Kent et al. 2015; monitoring costs set to 0	Disease monitoring resource use based on UK advisory board survey	██████	1.74	██████	██████
13	Disease monitoring frequency based on NICE guideline NG203	Disease monitoring frequency based on UK advisory board survey	██████	1.74	██████	██████
14	KRT threshold of eGFR ≤10 mL/min/1.73m ²	KRT threshold of eGFR ≤7.6 mL/min/1.73m ²	██████	1.74	██████	██████
15	Iptacopan SAEs counted as 9 individual events in 189.9 patient years	Iptacopan SAEs counted as 5 episodes in 189.9 patient years	██████	1.74	██████	██████

Footnotes: ^aScenario #3 should be interpreted with caution, since UK clinicians advised that predictions of SoC arm disease progression in this scenario lacked clinical validity (model-predicted median time to kidney failure with SoC 22.8 years, compared with approximately 10 years based on literature and advisors' clinical experience).^{4, 5}

Abbreviations: CKD, chronic kidney disease; CS, corticosteroid; CV, cardiovascular; eGFR, estimate glomerular filtration rate; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; QALY, quality-adjust life year; RaDaR, National Registry of Rare Kidney Diseases; SAE, serious adverse event; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SMR, standardised mortality ratio.

Sources: Go et al. 2004;¹⁰⁴ Jesky et al. 2016;⁶³ Kent et al. 2015;¹⁰⁵ Wong et al. 2024;¹⁰⁶ NICE (NG203). 2021. ³³

Validation

B 23. Clinical and health economic validation occurred during three meetings held between April 2022 and January 2025.

- a) Please provide reference 27: “Novartis. Data on File: Advisory Board Report - Clinical Interpretation of Data for Iptacopan in C3G. November 2024, 2024”.

This file has been provided within the reference pack ‘References_Data on File_v2.zip’, submitted through NICE Docs on 21st March 2025, under the file name “Novartis DoF_2024_Advisory Board Report_Clinical Interpretation of Data for Iptacopan in C3G.docx” (reference number 27 in the subsequently requested numbered reference pack ‘References_Data on File_v3.zip’, submitted through NICE Docs on 1st April 2025).

- b) The CS included summaries of the discussions held between December 2024 and January 2025 in the document “Clinical and Model Validation for Iptacopan in C3G”. In addition to these summaries, please provide the full minutes to these meetings.

The provided report represents the only written record of the discussions held; no separate minutes were produced.

B 24. The (results of the) technical validity assessments are not described in detail nor are detailed validation exercises (i.e. specific black-box tests) described in CS. The CS mentioned that “two checklists, based on the published TECH-VER checklist” were used for technical validation.

- a) Please provide a detailed description of the validity assessments performed as well as the results.

The model was validated by an independent team of health economists who were not involved in the original model development through two approaches. First, the internal validation checklist was completed to set up different scenarios ensuring the model responds appropriately; for instance, setting all utility values to 1 should make LYs equal QALYs. This process tests the model's reaction to extreme values. The internal validation checklist (adapted from the TECH-VER checklist to be more comprehensive) was completed twice – once upon review of the draft model developed by the global Novartis team (prior to adapting for the NICE submission) and once upon completion of the model adaptation for the NICE submission.¹⁰⁷ The initial checklist identified errors which were subsequently amended, while the final checklist identified no further errors.

Next, a detailed quality control was completed. This involved thoroughly reviewing every cell in the model to verify the correctness of all formulae, proper coding of macros, accurate referencing, absence of spelling or grammar errors, and consistent formatting.

- b) Please provide the filled-out TECH-VER checklist as well as any other checklist used for technical validation.

The completed checklists are provided within the reference pack included with the submission of the clarification questions response. The provided files include the initial internal validation checklist ('Clarification questions_internal_val_(Draft Global CEM)_Iptacopan in C3G_21Aug24') and the final internal validation checklist ('Clarification questions_internal_val_(Submitted NICE CEM)_Iptacopan in C3G_10Mar25') as well as the quality control checklist ('Clarification questions_technical_val_(Draft Global CEM)_Iptacopan in C3G_21Aug24'), detailing the checks performed in the model. Please note some errors and inconsistencies were corrected in the model rather than recorded in the form, however, the checklist illustrates the nature of the validation conducted.

B 25. Further external validation of modelled effectiveness would be desirable.

- a) Please report on the face validity of the model structure, modelling assumptions, model inputs, intermediate outcomes as well as final outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).
- b) Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using
 - I. evidence used to develop the economic model.
 - II. evidence not used to develop the economic model.

As noted in Section 3.13 of the CS, Novartis UK held two advisory boards with nine (April 2022) and ten (November 2024) UK clinicians with experience in treating patients with C3G in NHS clinical practice; insights from both advisory boards informed this submission.^{4, 50} Advisors provided their views on the current SoC and treatment landscape for C3G, level of unmet need, and iptacopan trial data, as well as clinical input for modelling disease progression and disease management before and after kidney failure.

Additionally, calls with two individual UK clinicians were conducted to clarify specific points of uncertainty relating to the submission, and model validation was undertaken in a joint call with one clinical and one external health economics expert from the UK.⁵ Model validation covered selection of the base case for modelling disease progression and treatment effect, health state utility values, health state costs, and AEs, as well as validation of clinical outputs of the draft economic model. Further input from two UK clinicians was obtained on a call conducted during the preparation of the clarification questions response.⁸

The modelling approach, inputs and assumptions presented in this submission considered the feedback received by clinical and health economics experts, as detailed throughout Section 3 of the CS. These calls confirmed the overall face validity of the modelling approach. Further discussion of the face validity of the model has been included throughout the responses within this document, with the responses to question B1–B20 providing further detail on the clinical plausibility and validity of the choices of model structure, assumptions, inputs, intermediate and final outcomes, in light of the evidence available, including the considerations and conclusions.

As noted in response to question B13 and B26, a TLR of previous NICE appraisals in CKD was conducted to gather potentially relevant input sources and consider potentially relevant modelling approaches. These responses therefore discuss the external validity of the model inputs, in light of evidence both used and not used to develop the economic model. The response to B26 includes page references for the full methodology and results of the TLR as detailed in the CS.

B 26. Please provide cross validations, i.e. comparisons with other relevant NICE TAs focussed on similar, potentially relevant, diseases (e.g. related NICE recommendations and NICE Pathways listed in the final scope) and elaborate on the identified differences regarding:

- a) Model structure and assumptions
- b) Input parameters related to:
 - I. Clinical effectiveness, i.e. time to CKD stage and eGFR slopes
 - II. Health state utility values
 - III. Resource use and costs
- c) Estimated (disaggregated) outcomes per comparator/ intervention
 - I. Life years
 - II. QALYs
 - III. Costs

As noted in Section 3.1 of the CS, given the lack of published cost-effectiveness studies in C3G, an additional targeted literature review (TLR) was undertaken of NICE technology appraisals (TAs) in chronic kidney diseases with final guidance published in the last 10 years, in order to support economic model development and inform potential sources for input values. The TLR methodology was described in full in Appendix E (Section E.2); briefly, a search of the NICE website was conducted on 13th December 2024, using an existing filter available on the website for NICE products on chronic kidney disease, for published TA guidance. The search identified 16 TAs. Among these, 3 TAs were excluded; TA482 was excluded since it focused on children and young people, while TA165 and TA117 were excluded since final guidance was published more than 10 years ago. None of the identified appraisals were for treatments for C3G.

For the 13 TAs included in the TLR, the information requested for items a) and b) is available in the CS and associated appendices:

- CS, Table 31: Key features of published NICE technology appraisals in chronic kidney diseases, pages 92–95
 - The same table can also be found in Appendix E, Table 11, pages 28–32

- CS, Table 42: Health state utility sources in previous NICE technology appraisals in chronic kidney diseases, page 111, provides a summary of sources used, with full details presented in:
 - Appendix F, Table 11: Utilities in previous NICE technology appraisals in chronic kidney diseases – CKD stages pre-KRT, pages 59–61
 - Appendix F, Table 12: Utilities in previous NICE technology appraisals in chronic kidney diseases – KRT (dialysis / transplant), pages 62–66
- CS, Table 44: Health state cost sources in previous NICE technology appraisals in chronic kidney diseases, pages 115–116, provides a summary of sources used, with full details presented in:
 - Appendix G, Table 12: Health state costs in previous NICE technology appraisals in chronic kidney diseases – CKD stages pre-KRT, pages 46–49
 - Appendix G, Table 13: Health state costs in previous NICE technology appraisals in chronic kidney diseases – KRT (dialysis / transplant), pages 49–61

The information requested for item c) is presented below in Table 52.

Table 52: Outcomes of previous NICE technology appraisals in chronic kidney diseases^a

TA (year)	Population	Intervention (I); Comparator (C)	Time horizon	Total costs	Total life years	Total QALYs
TA942 (2023) ²⁷	Adults with CKD	I: Empagliflozin in addition to individually optimised SoC C: Individually optimised SoC	50 years (lifetime)	I: £87,946.42 C: £93,406.65	I: 9.54 C: 8.48	I: 7.09 C: 6.24
TA937 (2023) ²⁸	Adults with primary IgAN at risk of rapid disease progression with a UPCR ≥ 1.5 g/g	I: Targeted-release (TR) budesonide in addition to SoC C: SoC	56 years (lifetime)	I: Redacted C: Redacted	I: 16.06 C: 15.96	I: Redacted C: Redacted
TA890 (2023) ⁸⁵	Adults with CKD-associated pruritus who are on haemodialysis	I: Difelikefalin in addition to established clinical management C: Established clinical management	42 years (lifetime)	I: Redacted C: £23,644	I: 4.65 C: 4.59	I: Redacted C: 2.75
TA882 (2023) ³¹	Adults with active lupus nephritis	I: Voclosporin in combination with MMF and low-dose CS C: MMF + CS C: Cyclophosphamide + CS C: Azathioprine + CS C: Rituximab C: Tacrolimus + MMF/CS	72 years (lifetime)	I: Redacted C: Redacted	I: Redacted C: MMF: 17.93 C: Low-dose cyclophosphamide (CYC): 17.53 C: High-dose CYC: 17.48 C: Azathioprine (AZA): 17.73 C: Rituximab (RTX) + MMF: 18.40 C: Tacrolimus (TAC) + MMF: 17.99 C: TAC: 18.04	I: Redacted C: MMF: 13.08 C: Low-dose CYC: 12.73 C: High-dose CYC: 12.69 C: AZA: 12.91 C: RTX + MMF: 13.49 C: TAC + MMF: 13.14 C: TAC: 13.19
TA877 (2023) ⁵³	Adults with CKD and type-2 diabetes mellitus	I: Finerenone in addition to SoC background therapy C: SoC background therapy	Redacted (lifetime)	I: £51,983 C: £50,204	I: 8.25 C: 8.12	I: 6.11 C: 6.01
TA825 (2022) ⁸⁶	Adults with anti-neutrophil cytoplasmic autoantibody-	I: Avacopan in combination with cyclophosphamide or rituximab C: Rituximab or cyclophosphamide in	40 years (lifetime)	I: Redacted C: £124,679	I: Redacted C: 9.30	I: Redacted C: 6.07

TA (year)	Population	Intervention (I); Comparator (C)	Time horizon	Total costs	Total life years	Total QALYs
	associated vasculitis (AAV)	combination with CS				
TA809 (2022) ⁸⁷	Adults with CKD awaiting a kidney transplant from a donor, who are highly sensitised	I: Imlifidase C: Dialysis	57 years (lifetime)	I: Redacted C: Redacted	I: Redacted C: Redacted	I: Redacted C: Redacted
TA807 (2022) ⁷⁹	Adults with symptomatic anaemia associated with CKD who are not dialysis-dependent at the time of treatment initiation	I: Roxadustat C: Erythropoiesis stimulating agents (ESA; modelled as a class)	25 years (lifetime)	I: Redacted C: Redacted	I: Redacted C: Redacted	I: Redacted C: Redacted
TA775 (2022) ²⁹	Adults with CKD	I: Dapagliflozin in addition to optimised SoC C: Optimised SoC alone (established clinical management)	Redacted (lifetime)	I: £56,526 C: £51,408	I: 9.26 C: 8.25	I: 6.80 C: 6.03
TA623 (2020) ⁶⁷	Adults with CKD stage 3-4 with hyperkalaemia (HK)	I: Patiromer C: No patiromer	35 years (lifetime)	I: Redacted C: Redacted	I: Redacted C: Redacted	I: Redacted C: Redacted
TA599 (2019) ³⁰	Adults with HK and an underlying condition of CKD or heart failure (HF)	I: Sodium zirconium cyclosilicate C: Standard care	80 years or initiation of KRT	Acute: I: Redacted C: Redacted Chronic: I: Redacted C: Redacted	Acute: I: 4.35 C: 4.27 Chronic: I: 5.99 C: 4.74	Acute: I: Redacted C: Redacted Chronic: I: Redacted C: Redacted
TA481 (MTA) (2017) ⁸⁹	Adult kidney transplant recipients	Overall 16 regimens modelled in MTA, including basiliximab, rabbit anti-human thymocyte/ antithymocyte (immune)globulin (ATG), tacrolimus, MMF, mycophenolate sodium, sirolimus, everolimus, belatacept, in	50 years	9 induction treatment combinations: range £90,794 to £102,320	Not reported	9 induction treatment combinations: range 10.7486 to 11.0344

TA (year)	Population	Intervention (I); Comparator (C)	Time horizon	Total costs	Total life years	Total QALYs
		combination with CS and ciclosporin and/or azathioprine		22 maintenance treatment combinations: range £90,794 to £235,490		22 maintenance treatment combinations: range 10.5773 to 11.2941
TA358 (2015) ²⁶	Adults with autosomal dominant polycystic kidney disease (ADPKD)	I: Tolvaptan C: No active treatment (no drug cost)	80 years (lifetime)	I: Redacted C: Redacted	I: 17.58 C: 16.76	I: 13.54 C: 12.63

Footnotes: ^aBase-case outcomes as reported in the respective company submissions (discounted).

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody-associated vasculitis; ADPKD, autosomal dominant polycystic kidney disease; ATG, rabbit anti-human thymocyte/antithymocyte (immune)globulin; C, comparator; CKD, chronic kidney disease; CS, corticosteroids; CYC, cyclophosphamide; ESA, erythropoiesis stimulating agents; HF, heart failure; HK, hyperkalaemia; I, intervention; IgAN, immunoglobulin A nephropathy; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; MTA, multiple technology appraisal; N/A, not applicable; NICE, National Institute for Health and Care Excellence; SoC, standard of care; TA, technology appraisal; TAC, tacrolimus; TR, targeted release; UACR, urine albumin-to-creatinine ratio.

Sources: Empagliflozin for treating chronic kidney disease (TA942);²⁷ Targeted-release budesonide for treating primary IgA nephropathy (TA937);²⁸ Difelikefalin for treating pruritus in people having haemodialysis (TA890);⁸⁵ Voclosporin with mycophenolate mofetil for treating lupus nephritis. (TA882);³¹ Finerenone for treating chronic kidney disease in type 2 diabetes (TA877);⁵³ Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis (TA825);⁸⁶ Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease (TA809);⁸⁷ Roxadustat for treating symptomatic anaemia in chronic kidney disease (TA807);⁷⁹ Dapagliflozin for treating chronic kidney disease (TA775);²⁹ Sodium zirconium cyclosilicate for treating hyperkalaemia (TA599);³⁰ Patiomer for treating hyperkalaemia (TA623);⁶⁷ Immunosuppressive therapy for kidney transplant in adults (TA481);⁸⁹ Tolvaptan for treating autosomal dominant polycystic kidney disease (TA358).²⁶

While none of the identified TAs covered interventions for C3G, information was considered as relevant during the development and parameterisation of the economic model for iptacopan in C3G. The iptacopan model uses a CKD stage structure, with CKD stage 5 denoted as pre-KRT and separate KRT states for dialysis and post-transplant. The overall 9 model health states are consistent with two previous recent appraisals in IgA nephropathy (TA937)²⁸ and CKD (TA775),²⁹ providing precedent for this model structure. Further appraisals have used CKD staging and/or separated KRT into dialysis and post-transplant health-states in different structures,^{26, 31, 53} further supporting the overall approach as a valid representation of a chronic kidney disease.

The base case economic analysis used APPEAR-C3G-derived efficacy and utility values for CKD stages 1–4, in line with the NICE preference for EQ-5D,²⁵ therefore supporting the validity of the approach. Efficacy was modelled using trial eGFR data, consistent with six of the appraisals identified in the TLR, although methods for generating transition probabilities varied.^{26-29, 53, 86} Only two of the prior appraisals used trial data to inform utility values;^{29, 53} while this is therefore an uncommon approach, the use of utility values generated from EQ-5D in the pivotal trial is considered a strength of this submission, since it reflects NICE's preference.²⁵

Utilities for CKD stage 5 (pre-KRT), dialysis, and transplant were sourced from published literature as no data were available from APPEAR-C3G. For CKD stage 5 (pre-KRT), a utility value from Jesky et al. 2016, a UK study which collected EQ-5D-3L data from 745 patients with CKD of any aetiology,⁶³ was used. This study was used as a source of utility data for CKD stage 5 in two previous appraisals,^{27, 28} and was used as a source of CKD stages 1–4, transplant and dialysis utilities in a third.⁶⁷ Due to its clinical relevance and precedent in other appraisals, Jesky et al. 2016 is therefore considered a valid source of utilities for the economic model. A scenario analysis used utility values from Jesky et al. also for CKD stages 1–4, with a limited effect on the ICER (■■■■%).

Dialysis and transplant utilities were sourced from Lee et al. 2005, a UK study estimating utility values for different KRT modalities from EQ-5D-3L collected in 416 patients.⁷⁶ Again this is a highly relevant source, and as such has been used in seven previous appraisals as a source of transplant and/or dialysis utilities.^{26, 27, 28, 29, 79, 85, 86}

Costs were sourced from NHS reference costs for dialysis and transplant (which account for the majority of healthcare resource use costs) in line with previous appraisals, and following the calculation methods as initially used in TA775 and subsequently adopted in TA942.^{27, 29} Additionally, post-transplant costs were based on an NHS Blood and Transplant fact sheet used in multiple previous appraisals (TA775, TA890, TA942).^{27, 29, 85} Transport costs for HD were estimated from Liu et al. 2015, as used in previous appraisals (TA937, TA809).^{28, 87}

Overall, due to the alignment to the NICE reference case and the use of UK-specific data from literature with precedent of use in multiple prior appraisals, the approach taken for these inputs is considered valid for decision making.

The deterministic base case results in this submission gave total LYs of 21.59 for iptacopan + SoC and 21.11 for SoC alone, and QALYs of 16.88 for iptacopan + SoC and 15.13 for SoC. The LYs and QALYs for both iptacopan + SoC and SoC were higher than both the intervention and comparator LYs and QALYs in previous appraisals, although a full comparison was not possible due to values in several published appraisals having been redacted (Table 52). However, due to the differences in disease, intervention, comparator, and time horizon, differences between these values were to be expected, with results of previous appraisals of limited relevance to the current submission.

The total costs for iptacopan + SoC were £[REDACTED] (updated company base case) and the total costs for SoC alone were £355,162, which were also greater than the total costs of interventions and comparators in the previous appraisals; however, it must be noted that nine of the 13 prior appraisals redacted total costs for the intervention, limiting the ability to conduct such a comparison. In addition, it should be highlighted again that previous appraisals covered different diseases, interventions, comparators, and time horizons, and as such a comparison of outcomes with previous appraisals is not considered meaningful.

[REDACTED]

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Single Technology Appraisal
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- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Kidney Research UK
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the country's leading kidney research charity. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice in the NHS and improve pathways and health outcomes for kidney patients. Our latest annual report 2023/24 shows the majority of our income is from donations, gifts, and legacies. The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are kidney patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Novartis - £40,500 (£7,500 Sponsorship of Scotland CKD Action Plan; £33,000 Sponsorship of Rare Kidney Conditions Report 2025) Alexion - £33,000 (Sponsorship of the Rare Kidney Conditions Report 2025)

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	To represent the views of patients, we held a focus group with two C3GN patients and the mother (carer) of a teenager with the condition. Because C3GN is an ultra-rare condition, there are very few patients and carers who can provide lived experience for this submission.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Because C3GN is an ultra-rare condition, patients and carers reported difficulties with getting a diagnosis in the first place. It took one patient some two years to achieve a diagnosis of C3GN. Currently in her fifties, she explained: “There were no treatments at that time, so even hearing that there’s a potential treatment is just so exciting. We so rarely hear about anything for us.” She described being put on steroids in her early twenties and being told not to eat anything with protein, salt or sugar, which meant ‘basically anything’. She started dialysis at 26 years old and received a kidney from her mother three years later. “I’ve been very lucky. I’m now 22 years post-transplant and I’ve not had the disease back. “I’ve never had children because there wasn’t enough information about whether I could pass it on.” Another patient currently in her 40s was diagnosed at age 14 years. Because she had been diagnosed relatively quickly and put on blood pressure medication, her native kidneys lasted well. About 10 years ago, whilst working in a senior role in London, she was suddenly told that she needed a kidney transplant. She underwent a successful transplant (with a kidney donated by her husband) which lasted for about 10 years.

	She had a second transplant in June last year from a deceased donor and is currently enjoying 'excellent' health: "I need to keep my mind strong and have brilliant people around me. I was encouraged not to let my disease stop me and was very lucky with my medical team. "When my first kidney failed, I was told to just go on holiday because they thought I would be restricted." The mother of teenage patient with C3GN described the difficulties of getting a diagnosis. Her son first developed symptoms – puffiness around his eyes – at age 10. Then he developed a lump in his neck which would not go away. Finally, he got an appointment with a paediatrician who ran blood and urine tests. The next day, they got a call from the hospital saying they thought her son had nephritis but needed further tests. Her son was tired and grumpy and had lost interest in life; it was hard to know whether this was due to illness or being a pre-teen. She said: "He is currently on the maximum dose of blood pressure tablets and mycophenolate as well. He still has proteinuria but is not classed a priority for any other treatments. "We don't want him to need dialysis or a transplant in the near future, but he will be quite low on the list of priorities for new treatments. That's a challenge for us." Patients and carers stress that living with C3GN is frightening; they face a lot of uncertainty in their lives. One commented: "If and when you get to end stage [kidney disease], you are always thinking 'please God, let this kidney work'. It's very frightening." They also feel alone; the condition is so rare there is 'no-one else to talk to about this exact thing'. One commented: "We get diagnosed at a very young age. When most of my friends were going out and having fun, I had to stay in and do 24-hour urine samples." Having C3GN can be an embarrassment, particularly for teenagers. The mum remarked: "It's hard handling the uncertainty and dealing with the sheer number of tests required all the time. We don't know if it's getting worse. Plus, all the other things around adolescence. Is it affecting his height etc.? There should be better reassurance and guidance." One patient commented: "This disease affects you at a young age and will affect you for the rest of your life. Whether you have a good transplant or not, it will still affect you. It impacts your schooling, career choice and

	where you live. I had to change careers and move house to be near a hospital. It puts you at an economic disadvantage and really contributes to health inequalities.” Another said: “Because it is rapid and aggressive, you can quickly get to end stage. This impacts your relationships. In the ‘90s, my friends were out raving; I was doing peritoneal dialysis. I saw my friends settle down with partners and have babies. At the same time, I was thinking can I survive another month?” Patients and carers recognised the impact of C3GN on black and minority groups, as well as those from lower socio-economic backgrounds who do not have good support networks around them. For the mum, her son’s diagnosis came as a big shock. She is constantly chasing: “Hospitals are not always great at communication, so I chase for test results, prescriptions and constantly have to follow up in case something gets missed. “Before diagnosis, there’s the early uncertainty. Because you haven’t got a ‘thing’, any single symptom could be serious.” School life can be challenging for children with C3GN: “I had to go to a parents’ evening with a piece of paper to ask every teacher to let him go to toilet and drink water. He’s on a low salt diet – so are school dinners suitable? I have to check up on what he’s eating. “Different levels of understanding can make it challenging. I need to be on first name terms with school nurse in case anything is going around, such as chicken pox.” Carers also experience an impact on their ability to work: “I’ve turned down job opportunities, because I might need to pivot. So, this also limits my career path.” For those patients who have reached kidney failure and have had a kidney transplant, there are other challenges: “We are dependent on medications generally available to transplant patients. Immunosuppression can make you vulnerable to things like COVID. You also need to be aware of longer-term conditions like kidney associated dementia, osteoporosis and other kidney-associated disease.”

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	All the patients and carers commented upon the inconsistencies of treatment and access to information. One patient remarked: “Patients need access to information and treatment. For example, the regime and experience of having a kidney transplant in London and Glasgow was completely different. “There’s not enough sharing. The US is ahead of the UK. I don’t think this is fair or reasonable. In 2025 there needs to be a better system about what is the best of the best. “With a renal rare disease, you need to become the expert of your own disease. I only know about research trials because I do the research myself. Nephrologists should be clued up and share best practice.” Patients and carers noted that after-care and access to services also need to improve, for example mental health resources.

8. Is there an unmet need for patients with this condition?	There are currently no available alternative treatments that target the underlying cause of C3GN. Patients want better treatments that are specific for their condition and more research into C3GN. They also want access to information and are keen to know their prognosis so that they can plan ahead. One patient explained: “Even if it’s bad, we need clarity so that can plan our lives. We need hope and we need to know the good news as well. “There’s a dearth of information. We don’t even know how many of us there are. Once you know what you are dealing with, you can find information. You really do feel alone. “I just wish there was more research because that immediately gives you hope. When I was in my 20s, I didn’t believe I would get to 35, so now I don’t have a pension. “A cure would be great. We don’t want ‘things to ‘tide us over’; we want medication and better treatments.” The mother added: “We are trying to find a way to control a situation that we have absolutely no control over. Very few people in the UK have gone through this. We’re trying to reassure my son whilst planning for the worst-case scenario. You don’t look down, but you don’t look away. “We have a big wait until ESRD. If there was something that specifically targeted the complement [system], it would make such a difference because he might not need a transplant.” Another patient remarked: “We don’t have another option. Always be mindful that life is precious and short.”

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patient 1 comments: "I think this is a super exciting development in such a rare kidney disease which I had for nearly three decades. The big advantage is that it's the first time ever there has been a drug available that actually treats the specific condition. I was 14 when I was first diagnosed, it was scary, things were uncertain and there was no treatment - no child or carer should have to hear that. They need hope of actual treatment that tackles the disease directly. To quote Carla Nester - "As a clinician treating young people living with C3G, I see firsthand the challenges with therapies used to treat this condition today, underscoring the vital need for dedicated treatment for these patients," said Carla Nester, M.D., M.S.A., F.A.S.N., Professor of Pediatrics-Nephrology at the University of Iowa and APPEAR-C3G Co-Investigator. "I am encouraged to see these data, which reinforce the clinically meaningful impact on kidney health measures we saw at 6 months. As the only oral complement inhibitor intended to treat C3G, Fabhalta could provide new hope for people living with this condition." Patient 2 comments: • The first advantage and one of the most important is: this gives patients hope.....that may not seem a practical advantage but for me being told there was no cure or treatment was devastating. Knowing there is a treatment that may help gives you a fighting chance, hope! • Reading the information, we have on this drug so far – this looks to be groundbreaking for patients in this group. In particular it helps with proteinuria within the first two weeks and over a year this becomes sustained and meaningful reductions. This is major news and an incredible improvement for these patients. The disease is rapid and progressive and this is a drug that can change this for patients. • This patient group are mainly children and young adults. The disease can mean needing dialysis and transplant within 5-10 years. This medication has the potential to change this. • Young transplant patients may need several transplants over the course of a lifetime, each transplant exposing them to more antigens and reducing the likelihood of finding a right match the next time – so anything that means it takes longer to get to a transplant stage may mean less dialysis and less transplants are needed over a lifetime. • Being young patients and being poorly with kidney disease and living with stage 4 or 5, dialysis and transplant means you lose time off school or reduced training opportunities, leading to inequalities when it comes to employment, salaries over a lifetime etc. - this medication not only slows the progression but improves the health of patients and I hope this means young people have opportunities to finish schooling and training, find better jobs. Maybe less dependence on being close to hospital.

	• Reading what this drug does is quite astounding actually. To know this medication exists and for patients not to have access to it would simply be wrong. • With the improvement in proteinuria this could mean patients may need less frequent routine visits and certainly reduced renal replacement therapies over their lifetime. • It is important to remember these patients will live their whole life with this disease. • Should a patient have a transplant the big risk is the disease returns in the transplant in 50% of cases, it is a rapid disease so this drug may revolutionise how long these transplants survive. Carer: "I would say the advantage would be that he [son] would be on a less broad immuno suppression and BP tablets, but that the downside would be the increased risk of certain bacterial infections."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patient 1 comments: “I don’t see any disadvantages for patients. I appreciate that there will be costs involved in making this available but when you consider the overall costs incurred during the lifetime of one kidney patient being prescribed multiple types of expensive drugs that don’t actually tackle the issue, dialysis and in most instances multiple transplants as reoccurrence of this disease happens in half of transplanted patients. I don’t think it makes financial sense not to make it available. That’s before you start to consider the potential economic impacts on having some of these patients being unable to work and contribute to society and potential mental health-related costs - this is something that must be pushed forward and made available to everyone who needs it.” Patient 2 comments: • This is a new medication so long-term data we won’t know but as the decline of proteinuria seems to stop and even improve with this medication this truly could change the life of these patients for the better. • Drug side effects is always a concern and can be hard to measure in a group that will have many symptoms from the disease itself, but this drug seemed to show no new symptoms. • Another problem can be that studies are hard in a rare disease group such as this so finding enough patients to join a study to reflect and show up all symptoms is difficult but it didn’t appear the AEs and SAEs were anything more than patients with this condition would expect or would be expected from the biopsy. • Side effects are common with the few other medications that all kidney disease patients take and often it is a compromise for patients - this medication would add to the tools available to the clinicians and if a patient didn’t tolerate it well, they may have to stop but this is normal life for a kidney patient. • Overall, for this patient group there are no real disadvantages in the drug itself. • Cost will probably be a disadvantage - this is an expensive medication, but it could change the whole life pathway of these patients; this medication could address directly many health inequalities. Carer: “The downside would be the increased risk of certain bacterial infections.”

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Younger patients have more to gain if the treatment prevents disease progression and ultimately the need for dialysis and / or transplantation.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/A

Other issues

13. Are there any other issues that you would like the committee to consider?	N/A

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• C3GN is a disease for life. Patients want a treatment that is specific to them and will stop progression of the disease, preventing the need for them to undergo dialysis and transplantation. • Because C3GN is an ultra-rare condition, diagnosis is often long and complicated and treatment is inconsistent. Patients feel very isolated. Accurate and relevant information is hard to find. Being a patient with C3GN, or caring for someone with the disease, can be extremely demanding, frustrating and time-consuming. • Having C3GN puts patients at enormous disadvantages in life. It impacts all aspects of a patient's life, from school and education choices, relationships and having a family, ability to work, choice of career, where you live and, as well as treatment, health and life expectancy. • Even if a patient has a successful transplant, other long-term conditions may affect them later in life. • The mental health-related impact of C3GN is significant for patients and their families and friends. Sufficient resources are not available.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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Single Technology Appraisal
Iptacopan for treating complement 3 glomerulopathy [ID6283]
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About you

1. Your name	
2. Name of organisation	MPGN/DDD Support group
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	The organisation is a support group for C3G patients and offers peer support to its members. Membership is currently 293
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	The organisation has had no funding from the company bringing the treatment to NICE, or any other comparator treatment companies in the last 12 months.
4c. Do you have any direct or indirect links	No.

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	- From conversations with patients and carers. - Personal Experiences

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with the condition varies from patient to patient, depending on the severity of the disease and its rate of progression to end stage renal failure. For someone with a slow rate of disease progression there might be very little impact on daily life for many years. Whereas for someone who has had rapid disease progression, and is at end stage renal failure, a life on dialysis has a huge impact on daily life. For patients with slow progression, and those who receive transplants, there is a severe anxiety associated with this diagnosis. The disease often recurs in transplants so patients must deal with not knowing when the disease may strike. This anxiety is made that much worse by the current lack of an effective treatment. Patients can feel like “a ticking time bomb.” If the C3G patient is a child, then the parent caring for that child has a huge impact on their life and their ability to remain in work. Children need a lot of extra care, can spend extended periods in hospital, and need to be accompanied to in centre dialysis treatment. Carers may also administer dialysis treatment at home, whether PD or Home HD, as the child will not be able to do this on their own. Caring for a patient with C3G is also mentally taxing. Carers will see the patient deteriorate over the course of many admissions, appointments and often procedures. Due to the current lack of effective treatments, patients do not tend to ever improve. The best-case scenario is usually stabilisation, for a time, before further deterioration.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	At present C3G progresses to end stage renal failure. There is currently no treatment to prevent this happening. At best current options delay this inevitability. Treatment for end stage renal failure is either dialysis or a transplant. The disease currently recurs in half of transplanted kidneys at the five year mark, which results in patients needing dialysis treatment or another transplant. Each time a C3G patient is transplanted, antibody sensitivity increases, which results in a smaller pool of potential donors for that patient. This means waiting longer for a suitable donor to be found and spending more time on dialysis. Long periods of dialysis are detrimental to overall health and lowers life expectancy for patients.
8. Is there an unmet need for patients with this condition?	Yes. Here is currently no cure for this disease. Some medications might slow down progression to end stage renal failure, but none prevent it.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and carers think that this technology will stop the disease and prevent patients reaching end stage renal failure, thus improving their quality of life by avoiding the need for dialysis and transplants. This technology provides a great deal of hope to patients and carers, where there has previously been none. Patients are optimistic about the advantage of this technology being a single, simple oral tablet. Some current treatments that have been attempted in patients have been long term courses of IV medications or treatments with high tablet burden or multiple severe side effects.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None reported.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients are generally treated depending on clinical presentation. In order to have a diagnosis, renal consultants would have been concerned enough to request a biopsy, which would indicate that renal function was compromised. Some of these patients will be managed conservatively, depending on renal function parameters. For patients who are maintaining stable, it could be argued that they might benefit less from the technology than for patients who are not remaining stable. Patients with rising creatinine, and worsening renal function would definitely benefit more from a technology that stopped the disease impairing kidney function. Transplanted patients, who have lost their native kidneys from C3G, might be another group who would benefit more from the technology than stable patients with the diagnosis. This would be to prevent the loss of the transplanted kidney. Halting the malfunction in the complement system that causes the disease would prevent damage to the kidney. Transplanted patients, who have lost previous transplanted kidneys from C3G, might be another group who would benefit more from the technology than stable patients with the diagnosis. This would be to prevent the loss of the transplanted kidney. Halting the malfunction in the complement system that causes the disease would prevent damage to the kidney.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Iptacopan has the potential to stop C3G damaging kidneys. • Quality of life would improve. No need for dialysis or transplantation. • Early intervention with Iptacopan post-transplant can stop damage to transplanted kidneys from occurring. • Iptacopan is the first effective treatment specifically targeting the mechanisms of C3G, offering new hope to patients •

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About you

1. Your name	[REDACTED]
2. Name of organisation	[REDACTED], on Behalf of UK Kidney Association
3. Job title or position	[REDACTED]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	<table><tr><td>Funder</td><td>Amount</td><td>Purpose</td></tr><tr><td>Novartis</td><td>£1,000.00</td><td>Conference sponsorship- SPR</td></tr><tr><td>Novartis</td><td>£4,440.00</td><td>Conference sponsorship- UKKW</td></tr><tr><td>Novartis</td><td>£2,400.00</td><td>Conference sponsorship- BAPN</td></tr><tr><td>Novartis</td><td>£73,394.00</td><td>RADAR</td></tr><tr><td>Novartis</td><td>£36,697.00</td><td>RADAR</td></tr><tr><td>Novartis</td><td>£52,416.00</td><td>RADAR</td></tr><tr><td>Novartis</td><td>£36,697.00</td><td>RADAR</td></tr><tr><td>Alexion</td><td>£2,400.00</td><td>Conference sponsorship- BAPN</td></tr><tr><td>Alexion</td><td>£1,500.00</td><td>Conference sponsorship- PNNG</td></tr><tr><td>Alexion</td><td>£2,400.00</td><td>Conference sponsorship- BAPN</td></tr><tr><td>Alexion</td><td>£1,000.00</td><td>Conference sponsorship- BAPN</td></tr><tr><td>Alexion</td><td>£1,200.00</td><td>Conference sponsorship- SPR</td></tr><tr><td>Alexion</td><td>£5,000.00</td><td>Conference sponsorship- BAPN</td></tr><tr><td>Alexion</td><td>£6,000.00</td><td>Conference sponsorship- BAPN</td></tr><tr><td>Amgen</td><td>£480.00</td><td>Conference registration- RPG</td></tr><tr><td>Samsung</td><td>£4,250.00</td><td>Conference sponsorship- UKKW</td></tr><tr><td>Samsung</td><td>£3,000.00</td><td>Conference sponsorship- RPG</td></tr><tr><td>Samsung</td><td>£3,500.00</td><td>Conference sponsorship- UKKW</td></tr></table>	Funder	Amount	Purpose	Novartis	£1,000.00	Conference sponsorship- SPR	Novartis	£4,440.00	Conference sponsorship- UKKW	Novartis	£2,400.00	Conference sponsorship- BAPN	Novartis	£73,394.00	RADAR	Novartis	£36,697.00	RADAR	Novartis	£52,416.00	RADAR	Novartis	£36,697.00	RADAR	Alexion	£2,400.00	Conference sponsorship- BAPN	Alexion	£1,500.00	Conference sponsorship- PNNG	Alexion	£2,400.00	Conference sponsorship- BAPN	Alexion	£1,000.00	Conference sponsorship- BAPN	Alexion	£1,200.00	Conference sponsorship- SPR	Alexion	£5,000.00	Conference sponsorship- BAPN	Alexion	£6,000.00	Conference sponsorship- BAPN	Amgen	£480.00	Conference registration- RPG	Samsung	£4,250.00	Conference sponsorship- UKKW	Samsung	£3,000.00	Conference sponsorship- RPG	Samsung	£3,500.00	Conference sponsorship- UKKW
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The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Patients with C3G currently have poor prognosis with median time to kidney failure estimated to be in the region 5-10 years. The average age of diagnosis is around 20 years old. There are high rates of disease recurrence with half of transplant grafts expected to be lost due to disease recurrence. There is therefore a high burden of kidney failure in patients with C3G There are key aims of treatment in C3G. Early treatment to stop progression of C3G and to minimise development of chronic kidney disease. Prevent or reduce progression to kidney failure due to untreated C3G and/or development of chronic kidney disease Delay impact of kidney failure to minimise lifetime risk and burden to patients. Prevent or reduce progression to kidney failure due to recurrence of C3G following kidney transplant
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in proteinuria of 30% at 6 months associates with slower eGFR decline and lower rates of kidney failure Caravaca-Fontan et al KI reports 2025. https://doi.org/10.1016/j.ekir.2025.01.024 Reduction in proteinuria of 20% associated with lower kidney failure risk Masoud et al https://doi.org/10.1101/2024.02.03.24301605

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Patients with C3G currently have poor prognosis with median time to kidney failure estimated to be in the region 5-10 years. The average age of diagnosis is around 20 years old. There are high rates of disease recurrence with half of transplant grafts expected to be lost due to disease recurrence. As a result, there is considerable lifetime risk of kidney failure in patients with C3G in spite of treatments described in section 9. There are no formally approved treatments for C3G. There is a high burden of kidney failure in patients with C3G which represents a huge unmet need for patients and healthcare professionals. C3G is ultra-rare, affecting 2-4 people per million per year so individual clinicians in secondary renal care may see cases very infrequently resulting in difficulties in disease recognition and management [see 9b on pathways]. Clinical trials address a group of patients with proteinuria and reasonable kidney function [urine P:CR > 100mg/mmol and eGFR>30], however one group who may have even worse prognosis are the group of patients with eGFR<30 have acute inflammatory renal disease, often crescentic who have potential for recovery but were excluded from clinical trials [eGFR<30, rapidly progressive GN].

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Supportive treatments including inhibition of the renin-angiotensin system with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for management of chronic kidney disease due to C3G. More recently, some clinicians will add in a sodium glucose co-transporter 2 inhibitors (SGLT1i) for management of chronic kidney disease due to C3G. If significant proteinuria [proteinuria >1g/day] and/or declining kidney function, immunosuppression with mycophenolate mofetil and corticosteroids. Choice of immunosuppression with mycophenolate and steroids is based on observational data only. In recent years, some patients were enrolled into clinical trials of complement inhibitors instead of starting immunosuppression; others were enrolled into clinical trials of complement inhibitors after inadequate responses following immunosuppression.

	In refractory cases, clinicians sometimes try other immunosuppression, not limited to cyclophosphamide, rituximab, plasma exchange or eculizumab [Wong et al cJASN 10.2215/CJN.00320121]. These treatments [aside from eculizumab] are not listed in most recent KDIGO guidelines. In post-transplant recurrent C3G, the high proportion of patients that develop recurrence do so despite immunosuppression that has been commenced as part of transplantation standard of care to reduce risk of allograft rejection. These patients are likely to lose their transplant allografts. In a minority of patients with aggressive recurrence may be considered for eculizumab under the NHSE clinical commissioning policy 16054/P. Long-term outcomes in those patients who have received eculizumab for this indication appears to be poor based on the experience of the national renal complement therapeutics centre. Eculizumab is not funded in the NHS for patients without kidney transplants.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases https://doi.org/10.1016/j.kint.2021.05.015 NHSE Clinical commissioning policy for post-transplant recurrence of C3G. https://www.england.nhs.uk/wp-content/uploads/2017/02/clin-comms-policy-16054p.pdf
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Referral to secondary care is standard for onset of proteinuria, CKD and AKI that are possible clinical presentations of C3G. C3G is one of a few differentials of kidney disease that may be made following kidney biopsy, a routine test in secondary care. If C3G is diagnosed or suspected following initial biopsy review: Specialist complement testing and differentials of C3G including paraprotein related disease is taken into consideration. This is often in combination with onward referral to expert centres for second opinions Variation can include:

	threshold for kidney biopsy – ie not enough proteinuria or perception of too much chronic damage to justify biopsy. Failure to diagnose C3G could impact future treatment options or consideration of recurrence risks following transplant. Discussion with expert centres with a specialist interest in C3G [though for patients with recurrent C3G, the NHSE policy focuses referrals to the National Renal Complement Therapeutics Centre for consideration of eculizumab]. Access to complement testing [eg nephritic factors, anti-FH antibodies, genetics] to look for abnormalities of the complement system that associate with C3G. Staining techniques in renal pathology may alter therefore making more difficult to make a diagnosis of C3G. Access to special stains in renal pathology that might reveal key differential diagnosis of C3G eg pronase digest to look for evidence that C3G is due to a paraprotein.
9c. What impact would the technology have on the current pathway of care?	Clinicians will review prevalent patients who have ongoing clinically significant proteinuria and ongoing risk of kidney failure and carefully assess incident patients who may have a diagnosis of C3G. Clinicians may refer a higher proportion of C3G or suspected C3G cases for specialist review, specialist complement testing and pathology review at an expert centre, to increase confidence of a C3G diagnosis or conversely, more confidently exclude a diagnosis of C3G.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is an oral therapy that is currently being used by some patients within ongoing clinical trials and compassionate use in C3G. It is already being used in PNH. It would be used alongside supportive treatments such as ACEi/ARB in keeping with entry criteria into clinical trials. Clinicians would then likely choose iptacopan versus mycophenolate or corticosteroids as next line therapies which would reflect clinical trial entry criteria. The absence of controlled data to support the use of mycophenolate and steroids compared to the available data for iptacopan may influence decision making in favour of iptacopan.
10a. How does healthcare resource use differ between the technology and current care?	Iptacopan is taken orally so not different to supportive care (ACE/ARB) or initial immunosuppression [mycophenolate / steroids], which are also oral. Treatments that are infrequently used and not a significant comparator to iptacopan include Rituximab, cyclophosphamide and eculizumab. These would be intravenous. Plasma exchange would be more

	intensive and require a vascular catheter, plasma products and nursing expertise to deliver the treatment. Again this would not be a comparator for iptacopan. Clinical diagnosis and testing as before but potentially a greater emphasis on seeking expert opinion given rarity of disease and unfamiliarity of clinicians with C3G and iptacopan. There is also a requirement for vaccinations to mitigate against risk of infection against encapsulated organisms and meningococci.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Initial diagnosis or suspected diagnosis will be made in secondary care but expert opinion or testing may be in specialist centres as per 9b. Once decision to start treatment has been made, prescription of iptacopan could be made by secondary care as part of a shared care model with expert specialist centres.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Consideration of making existing diagnostic tests, clinical expertise more readily available to secondary care in the diagnosis and management of C3G. These tests and expertise will not be available in secondary care. Resource will be required to access. Specifically, in order to increase availability of existing diagnostic tests, it may be necessary to transport biopsy tissue / slides and blood samples for specialist tests to expert centres. Most notably complement testing eg nephritic factors, anti-FH antibodies, genetics that are only available at a single site, the National Renal Complement Therapeutics centre. In addition, some of these blood tests require additional processing at referring centres and transport to diagnostic laboratories on dry ice.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
11a. Do you expect the technology to increase length of life more than current care?	Yes. Targeting the underlying mechanism of disease, reduces impact of disease on kidney function and delays time to kidney failure that associates with morbidity and mortality.
11b. Do you expect the technology to increase	Yes. Targeting the underlying mechanism of disease, reduces impact of disease on kidney function and delays time to kidney failure that associates with morbidity and mortality.

health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with acute highly inflammatory C3G. These were excluded from trials due to the acute nature of disease, often with low eGFR in the acute phase of disease. These may have excellent well-preserved kidneys. It is possible these patients have more to be gained if the treatment works in this cohort. Patients with slow indolent decline in kidney function who have pre-existing irreversible kidney disease by the time of diagnosis. These were also excluded from clinical trials and may not benefit as much as other patients.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Iptacopan is a taken orally and is comparable to other medications that patients may be using. There is need to consider risks of infection [mandatory vaccination against pneumococci, haemophilus influenzae type b and also meningococci], patient vigilance and consideration of additional prophylactic antibiotics. Monitoring of clinical parameters would be standard as per starting any therapy however measuring effect of iptacopan on the complement system may require additional tests compared to current standard of care including some samples that require transport to specialist labs using dry ice.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	Yes. Review of clinical parameters and biopsy as a minimum to start treatment. Review of the complement system would increase confidence of a complement-mediated process if diagnosis of C3G is otherwise unclear.

include any additional testing?	Treatment would be stopped patient processed to kidney failure. Other reasons for stopping may be considered if treatment not thought to be effective eg no impact on progressive kidney failure or failure to regulate the complement system. Collection and review of post-treatment would be valuable in stratifying clinical response that may help justify additional stopping criteria. A programme of research to explore additional stopping criteria including in patients who initially benefit could help determine optimal treatment duration. For example, robust detection of specific abnormalities that dysregulate complement that if no longer present, may mean complement inhibitory therapies such as iptacopan are no longer required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Some patients might have improvements in symptomology due to nephrotic syndrome and reduced risk of complications of nephrotic syndrome that include oedema, risk of infection and thromboembolic events.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. As per 16a and 16b.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. Iptacopan inhibits the alternative pathway of complement which is part of the underlying disease mechanism in C3G. It therefore provides a specific targeted for patients with C3G for the first time. It demonstrates statistically significant reduction in proteinuria, in a double-blinded randomised control trial over and above current standard of care.

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. There is therefore a high burden of kidney failure in patients with C3G which represents a huge unmet need for patients and healthcare professionals. Iptacopan reduces proteinuria by targeting the mechanism of action in disease. The outcome is preserving kidney function and at worst delaying and at best preventing kidney failure, depending upon the extent of any irreversible damage that has been sustained at the point of starting treatment. In patients who have already reached kidney failure and require dialysis, the mechanism of action in disease is comparable so treatment following transplant will likely reduce the impact of C3G on the renal allograft. As stated previously, this is based on extrapolation due to comparable mechanisms of action in disease rather than specific trials in this clinical group.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Based on the safety data reported in the phase 2 and phase 3 clinical trials of iptacopan in C3G, iptacopan appears to be well-tolerated. Due to the mechanism of action of iptacopan, there is likely to be a higher risk of infection due to encapsulated organisms and meningococci. As part of the clinical trials, there is a vaccinations schedule to help mitigate risk of infection. In the clinical trials, only a small number of patients have had infections due to encapsulated organisms and were treated with antibiotics.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes in so far as there is a prevalent cohort of patients with C3G in the UK who have ongoing proteinuria [typically urine P:CR >100mg/mol] and eGFR >30/min. Patients who have less proteinuria are likely to be at lower risk of kidney failure. However, patients with eGFR <30 fall into two categories – those who have significant chronic kidney disease in whom we wouldn't routinely offer immunosuppression currently and who were not included in trials. The group of patients with eGFR<30 have acute inflammatory renal disease, often crescentic who have potential for recovery but were not eligible for clinical trials. There would be an ongoing unmet need

	in this group. As C3G is a very heterogenous group of patients, some patients including a rare group of patients with CFHR5 nephropathy, a genetic subset of patients were not captured in the phase 2 and phase 3 trials. The predominant data from the phase 2 study and all data from the phase 3 study excludes post-transplant recurrence of C3G.
18a. If not, how could the results be extrapolated to the UK setting?	For transplant – mechanism of disease is comparable. In transplant, there is the opportunity for prospective monitoring for recurrence permitting treatment at the earliest opportunity therefore maximising potential to preserve renal allograft function.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Proteinuria reduction, stabilisation of eGFR demonstrate clinical impact. Improvements in serum C3, reduction in C3 staining on biopsy and reductions in disease activity on biopsy help infer mechanism of action. All were measured in the trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Proteinuria reduction is being shown to associate with stabilisation of eGFR and lower rates of kidney failure. Reduction in proteinuria of 30% at 6 months associates with slower eGFR decline and lower rates of kidney failure Caravaca-Fontan et al KI reports 2025. https://doi.org/10.1016/j.ekir.2025.01.024 Reduction in proteinuria of 20% associated with lower kidney failure risk Masoud et al https://doi.org/10.1101/2024.02.03.24301605
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that	No.

might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	Real-world experience largely reflects compassionate use. This includes patients that fell outside of clinical trial criteria and also additional patients with recurrent C3G following transplant. Reports are limited but include a patient with proteinuria, lower eGFR than 30ml/ min who did not have 3 months stable treatment on immunosuppression who showed proteinuria reduction and improvements in eGFR following treatment with iptacopan [https://doi.org/10.1093/ndt/gfae069.457]. In another report, two patients who had proteinuria and worsening eGFR due to transplant recurrence demonstrated improvements in proteinuria and stabilisation in eGFR following treatment with iptacopan [10.1016/j.xkme.2024.100823].

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• C3G has a high unmet need with high rate of progression to kidney failure despite currently available treatments • C3G has a high unmet need amongst patients who require, or have had a kidney transplant. • Iptacopan demonstrates clinically significant treatment response of reduction in proteinuria as shown in the phase 3 randomised control trial is likely to reduce long-term rates of kidney failure. • The clinical trial population fairly reflects the native C3G cohorts in the UK and can be extrapolated to transplant cohorts due to comparable mechanisms of disease. • Iptacopan is well tolerated in the clinical trial cohort with clear mitigation strategies with respect to risk of infection due to encapsulated organisms and meningococci.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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The information that you provide on this form will be used to contact you about the topic above.

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Single Technology Appraisal
Iptacopan for treating complement 3 glomerulopathy [ID6283]
Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	██████████
2. Name of organisation	UK Renal Pharmacy Group (part of the UKKA)
3. Job title or position	██████████
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? No A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.

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The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To attest or markedly slow disease progression developing to a more advanced stage of Chronic Kidney Disease (CKD) and/ or kidney failure requiring kidney replacement therapy (e.g. a form of dialysis and/ or a kidney transplant).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Stabilisation or improvement of excretory kidney function. Significant reduction in proteinuria. Significant increase in serum C3 from baseline after 12 months of treatment. Increase in serum albumin (if clinically significantly low due to nephrotic range proteinuria). All the above sustained over a period of years.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Currently treatment usually looks like: Native or transplant kidney biopsy. The evidence base for treatments in C3 glomerulopathy is limited. Standard of care consisting of: ACE inhibitor/ Angiotensin Receptor Blocker

	Blood pressure optimised. Serum lipids optimised. Mycophenolate mofetil/ mycophenolate sodium +/- prednisolone. SGLT2 inhibitor (no definitive trial evidence) Regular monitoring of kidney function including excretory kidney function, proteinuria, serum albumin. Likely or confirmed cases of C3 glomerulopathy to be discussed with National Renal Complement Centre (NRCTC) in Newcastle. NRCTC will undertake genetic and immunological evaluation of the complement system that may be useful in the investigation of C3 glomerulopathy. NHS England have approved funding for the use of eculizumab in the treatment of recurrence of C3 glomerulopathy post-kidney transplant (NHS England: 16054/P). Eculizumab is not funded by the NHS in England for treatment of C3 glomerulopathy in native kidneys. Eculizumab is unlicensed for treatment of C3 glomerulopathy.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	For recurrence of C3 glomerulopathy in a transplant kidney only: Clinical Commissioning Policy: Eculizumab in the treatment of recurrence of C3 glomerulopathy postkidney transplant (all ages); NHS England: 16054/P. There are no NHS clinical guidelines for C3 glomerulopathy in a native kidney. NICE produced an evidence summary for C3 glomerulopathy in the native kidney: eculizumab in Dec 2015; NICE: ESUOM49. KDIGO 2021 Guideline for the Management of Glomerular Diseases includes C3 glomerulopathy in Chapter 8: Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	Defined via NRCTC guidance. There can be occasional delays in accessing expertise in the pathology of C3 glomerulopathy..

experience is from outside England.)	
9c. What impact would the technology have on the current pathway of care?	To attest or markedly slow disease progression developing to a more advanced stage of Chronic Kidney Disease (CKD) and/ or kidney failure requiring kidney replacement therapy (e.g. a form of dialysis and/ or a kidney transplant). In the current NHS England pathway for C3 glomerulopathy recurrence in a transplant kidney the treatment with eculizumab is only funded for four months and then requires a period three to four months of watchful waiting before a further course of treatment may be accessed. This potentially leads to further loss of kidney transplant function and progression of chronic kidney disease. In cases where there is a good response to eculizumab there is no commissioned way to continue treatment without a treatment break. Iptacopan would be a long-term treatment of C3 glomerulopathies in both native and transplant kidneys.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be new and additional to current care in NHS clinical practice. A secondary potential outcome is that potentially more people with C3 glomerulopathy who have progressed to an advanced stage of CKD and/ or require a form of dialysis will be able to consider a living kidney donor transplant in the knowledge that iptacopan will attest or markedly slow disease progression should there be recurrence in the transplant kidney. Approximate rate of recurrence of C3 glomerulopathy is 50 to 80% post kidney transplant.
10a. How does healthcare resource use differ between the technology and current care?	Similar. May be some additional outpatient visits and monitoring around the time of commencing iptacopan. Some additional initial visits to primary and secondary care for vaccination against encapsulating bacteria prior to commencing treatment.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care.
10c. What investment is needed to introduce the technology? (For example,	Iptacopan's Medicines and Healthcare products Regulatory Agency (MHRA) Risk Management Programme (RMP) for iptacopan is similar, if not less restrictive, for that of eculizumab. NRCTC specialist centre expertise likely to be similar.

for facilities, equipment, or training.)	Potentially there may need to be improved access to/ responsiveness from, or resource for expertise in the pathology of C3 glomerulopathy.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
11a. Do you expect the technology to increase length of life more than current care?	Yes.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	With respect to treatment after standard of care i.e. in comparison to eculizumab: Easier. Iptacopan is an oral twice daily hard capsule. Vaccination requirements like those for eculizumab. There can be challenges in accessing vaccination in primary care for meningitis B; meningitis A C, W135 and Y; and Haemophilus influenzae type B and Neisseria meningitides group C vaccine. Additionally, Haemophilus influenzae type B and Neisseria meningitides group C vaccine is only licensed in children under 2 years of age.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Likely pathway will follow current NRCTC guidance with addition of NICE TA when published.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Reduction in progression to advanced CKD. Reduction in progression to kidney failure requiring kidney replacement therapy (e.g. a form of dialysis and/ or a kidney transplant). Increased survival time of transplant kidney in cases of kidney transplantation in a person with C3 glomerulopathy. Increased support for living kidney donation to a person with C3 glomerulopathy in knowledge that there is a treatment to attest or markedly slow disease recurrence, if occurs, in the transplant kidney.
16a. Is the technology a 'step-change' in the	Yes. Iptacopan will be the first licensed treatment beyond current standard of care (which is not disease modifying in most cases).

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Hyperlipidaemia is an undesirable effect of iptacopan. Optimisation of serum lipids is potentially a standard of care for treatment of C3 glomerulopathy.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, for C3 glomerulopathy in transplant kidney. No, for C3 glomerulopathy in native kidney; there is no disease modifying technology commissioned.
18a. If not, how could the results be extrapolated to the UK setting?	Yes
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Stabilisation or improved excretory kidney function. Reduction in urine proteinuria. UPCR from baseline; and $\geq 50\%$ Significant increase in serum C3 from baseline after 12 months of treatment.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not used.

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	To date, no.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. How do data on real-world experience compare with the trial data?	Unknown.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Hugely needed targeted treatment for shutting off C3 glomerulopathy disease. • Iptacopan will attest or markedly slow progression of C3 glomerulopathy. • Quality of life for people with C3 glomerulopathy markedly enhanced through a long-term targeting disease modifying treatment sustained. • Increased survival of transplant organ in cases of C3 glomerulopathy recurrence. • Overcomes perceived inequality with eculizumab for recurrence in kidney transplant when stabilising and/ or showing clear disease regression for it to be stopped for a period of up to 4 months watchful waiting.

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Single Technology Appraisal
Iptacopan for treating complement 3 glomerulopathy [ID6283]
NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	NHS England
3. Job title or position	

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality-of-service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England commissions a highly specialised service for aHUS from the national centre in Newcastle. An objective of this service is to provide advice to clinicians on other complement related renal disorders including C3 glomerulopathy. NHS England has commissioning responsibility for the service specification and policies for aHUS and C3G as retained services as defined within the Manual of Prescribed Specialised Services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	No guidelines.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not clearly defined. Provision of advice is set out in the service specification for aHUS but treatment options for this group of patients is limited and the current management oversight provided in Newcastle currently is for a subset of C3G patients https://www.england.nhs.uk/wp-content/uploads/2017/04/atypical-haemolytic-uraemic-syndrome-all-ages.pdf NHS England also has a published routine commissioning policy on the use of eculizumab in the treatment of recurrence of C3G post kidney transplant and a not routinely commissioned policy on the use of eculizumab in the prevention of recurrence of C3G post kidney transplant https://www.england.nhs.uk/wp-content/uploads/2017/02/clin-comms-policy-16054p.pdf https://www.england.nhs.uk/wp-content/uploads/2018/07/Eculizumab-in-the-prevention-of-recurrence-of-C3-glomerulopathy-post-kidney-transplant.pdf Initial discussions suggest there is broad clinical consensus on the pathway of care required to best manage this group of patients.
8. What impact would the technology have on the current pathway of care?	The pathway of care would need to be formalised and commissioned for C3G

The use of the technology

9. To what extent and in which population(s) is the technology being	The current highly specialised service pathway manages a small subset of C3G patients, the wider cohort of C3G patients is managed in local renal centres

used in your local health economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Very limited current treatment for this patient group.
10a. How does healthcare resource use differ between the technology and current care?	A commissioned diagnostic and management pathway will be required to facilitate patient access to the new treatment if approved. It is anticipated this will require additional healthcare resource, not yet quantified.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Anticipated tertiary pathway for diagnosis and management advice with shared care with secondary renal services is likely to be the main route for prescribing and monitoring. The clinical model would need further discussion and agreement within NHS England. In addition, vaccination against <i>Neisseria meningitidis</i> and <i>Streptococcus pneumoniae</i> is expected to be required for all patients with vaccination against <i>Haemophilus influenzae</i> type B recommended.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Not quantified, the expectation is that a diagnostic and management service will need to be established.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Not in current use.
11. What is the outcome of any evaluations or	Not evaluated, not in current use.

audits of the use of the technology?	

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	The disease affects people of all ages, starting in childhood and young adulthood, men and women are equality affected. No equality issues have been identified.
12b. Consider whether these issues are different from issues with current care and why.	NA

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Single Technology Appraisal

Iptacopan for treating complement 3 glomerulopathy [ID6283]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

Iptacopan for treating complement 3 glomerulopathy [ID6283]

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send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on 2 July 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating complement 3 (C3) glomerulopathy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	David Kavanagh
2. Name of organisation	Newcastle University/ The Newcastle upon Tyne Hospitals NHS foundation trust. National Renal Complement Therapeutics Centre
3. Job title or position	Professor of Complement Therapeutics/Honorary Consultant Nephrologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with C3 glomerulopathy? ☒ A specialist in the clinical evidence base for C3 glomerulopathy or technology? ☒ Other (please specify): Research in basic /clinical science on C3G
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (I have not seen any submission)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

Clinical expert statement

Iptacopan for treating complement 3 glomerulopathy [ID6283]

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8. What is the main aim of treatment for C3 glomerulopathy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Ultimately the aim of treatment with C3G is to stop end stage kidney failure, however, it is not feasible to evaluate this in clinical trials as progression to end stage kidney failure occurs over a 10-15 year period in ~50%. This problem with clinical endpoints was specifically addressed in C3G by the Kidney Health Initiative (KHI), a public–private partnership between the American Society of Nephrology and the US Food and Drug Administration (FDA). For a more detailed summary- Clin J Am Soc Nephrol. 2024 Sep 1;19(9):1201-1208). This expert panel assessed the currently available data supporting the efficacy end points (1) proteinuria, (2) eGFR, and (3) histopathology. In essence, in a disease where the pathophysiology of disease is exquisitely known (i.e. activation of the alternative pathway {AP} of complement), blockade of the AP associated with a favourable effect with lowering of proteinuria, stabilization, in eGFR and improved histologic changes provides convincing evidence of efficacy, They specifically noted that complete alignment of all 3 end points would not be required.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	The KHI reviewed the evidence for treatment thresholds and concluded that there was a lack information on the minimum thresholds for change in any of the three end points (1) proteinuria, (2) eGFR, and (3) histopathology that would be considered clinically meaningful in C3G.

	With regards to the primary endpoint of the trial- a significant reduction in proteinuria- it is known from natural history studies that decrease in proteinuria between 0-12 months was associated with lower kidney failure risk.
10. In your view, is there an unmet need for patients and healthcare professionals in C3 glomerulopathy?	Yes. There is currently no treatment with good evidence for efficacy in C3G.
11. How is C3 glomerulopathy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Current standard of care would rely on supportive treatments (e.g., blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors or AT1-receptor blockers) with or without mycophenolic mofetil (MMF) and corticosteroids. Standard of care is based on these guidelines -Kidney Disease: Improving Global Outcomes Glomerular Diseases Work G. KDIGO 2021 Clinical practice guideline for the management of glomerular diseases. <i>Kidney Int</i> 2021; 100: S1–S276. There is general agreement on the current standard of care. Blockade of the renin-angiotensin-aldosterone system would be considered routine for most proteinuric renal diseases. MMF and corticosteroids are given however there is general agreement that the evidence for their use is poor- based on retrospective uncontrolled studies.

	The new technology would replace MMF and corticosteroids . Blockade of the renin-angiotensin-aldosterone system would remain as part of the treatment with iptacopan
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Iptacopan would replace MMF and corticosteroids . The data available from trials would suggest that this will delay or possibly prevent progression to end stage kidney failure. This would prevent dialysis and the need for renal transplant. The disease relapses in ~80% post renal transplant and the trial data suggests that treatment with iptacopan would delay failure of the transplant. This agent should be used in the setting of a highly specialist service. Key investments will be 1) improved pathology services to ensure correct diagnosis 2) improved complement diagnostics (e.g. C3, C4 & C5 Nephritic factors and complement component Abs) to allow adequate dosing and cessation (e.g. if nephritic factor titre wanes) 3) mechanism to ensure adequately vaccinated against meningococcal disease- although this is an extension of the service already provided for eculizumab /ravulizumab use in aHUS
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.

Clinical expert statement

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The clinical trials of iptacopan in C3G does provide evidence of clinically meaningful benefits compared to current standard of care. The data suggests that iptacopan will delay progression of renal failure (both in native and post-transplant disease) and the need for dialysis. It is an extrapolation to comment on any increase in life expectancy based on short term studies with proteinuria as the primary end point although it is not an unreasonable assumption to make that preventing end stage renal failure will increase length of life. I would expect improved quality of life on iptacopan vs standard of care based on delaying progression of renal failure. It should be noted that in the phase 3 trial of iptacopan the FACIT –Fatigue scores were in the normal range at baseline for both treatment and control arm and there was no significant change observed. My explanation for this that the trial has patients very early in disease course (mean eGFR 94.1) and I would only expect quality of life score to be impacted when the later stages of kidney disease are reached. Thus slowing progression would be predicted to ultimately improve quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The pathophysiology of disease is well understood (i.e. activation of the AP of complement) and therefore the therapy (therapeutic blockade of the AP) would be expected to work in all individuals including those with recurrence post renal transplant.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	Iptacopan is an oral tablet and as such will be as easy for patients to take.

Clinical expert statement

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	We would suggest prophylactic antibiotics, which would not normally be given with standard of care-corticosteroids & MMF. This would be an extra tablet Vaccination would be required; a measurement of vaccination titre; and revaccination as required. This is not currently performed with MMF and corticosteroids .
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There should be rules for starting and research to determine drug cessation. Starting therapy will be based on initially a renal biopsy. Renal pathology services will need alignment across the UK as currently the gold standard tests to diagnose C3G are not available in all. I would suggest a group of 3 renal pathologist in the UK to review any biopsy prior starting treatment. There will be exclusion criteria based around secondary causes of C3G (e.g. infection, monoclonal gammopathies etc) NICE should dictate a programme of research to determine when the drug should be stopped prior to end stage kidney failure. Currently there is no data on drug cessation and, given the pathogenesis of disease, long term treatment may be required. As the majority of C3G cases are secondary to autoantibodies to complement proteins if the autoantibodies waned over time, it could be predicted that the drug could be stopped. This would require additional autoantibody tests. Although obvious, it is probably worth stating that, if the patient reaches end stage kidney failure, iptacopan should be stopped.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I am not an expert in health economics / QALY calculations and cannot comment on this.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	This is a step change in the management of C3G. Until now there was no treatment that was shown to improve outcome for patients with C3G. The phase 3 trial of iptacopan was the first trial to ever meet its primary endpoint in this condition. As such there is a large unmet need.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile appears relatively benign from the trial data. There is the potential risk of meningococcal sepsis from complement blockade but this risk is known and manageable with prophylactic antibiotics and vaccination. It is notable that there were no cases on meningococcal sepsis in the trials.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials?	The trials contained a large number of UK patients, so the trial is a good representation of UK practice. The most important outcomes from this trial are

Clinical expert statement

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	1) The significant improvement in proteinuria. It is known from natural history studies that decrease in proteinuria between 0-12 months was associated with lower kidney failure risk. Kidney International 2025 (https://doi.org/10.1016/j.kint.2025.06.003.) 2) The stabilisation of the eGFR slope. Natural history data (RaDaR, GLOSSEN registries) suggests that stabilization of eGFR slope would be expected to decrease the risk of kidney failure. 3) The improvement in serum C3 level. This speaks of the mode of action of the drug with regards to the disease pathogenesis. I am not aware of any data linking this marker to long term outlook however it is important as it demonstrates that the drug is doing what we expect i.e blocking the complement activation that causes disease. The normalisation of C3 suggests that we are stopping the cause of disease- especially in the context of reduced proteinuria and eGFR stabilization I am not aware of any other adverse effects out with the clinical trials and iptacopan is used in PNH currently.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real world data in C3G is limited however in the C3G patients given compassionate use the response seems at least as good as in the trial. The safety profile in PNH appears similarly benign.

Clinical expert statement

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Data currently does not include paediatric patients although a study is underway.

I do not think there any other equality issues

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is a high unmet need for patients with C3G with no treatment known to work

The reduction in proteinuria is significant and from natural history studies will decrease the risk of kidney failure.

The stabilisation of eGFR appears significant and from natural history studies will decrease the risk of kidney failure

Iptacaopan has a beneficial safety profile in C3G

The totality of evidence suggests that iptacopan should be used with blockade of the renin-angiotensin-aldosterone as first line treatment in both native and transplant recurrent C3G

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Single Technology Appraisal

Iptacopan for treating complement 3 glomerulopathy [ID6283]

Clinical expert statement

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Thank you for your time.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating complement 3 (C3) glomerulopathy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Matthew Pickering
2. Name of organisation	MPGN/DDD Support group
3. Job title or position	Professor of Rheumatology and Wellcome Senior Fellow in Clinical Science, Imperial College London Honorary Consultant Rheumatologist, Imperial College Healthcare NHS Trust
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with C3 glomerulopathy? ☒ A specialist in the clinical evidence base for C3 glomerulopathy or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for C3 glomerulopathy?	To prevent kidney failure

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(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Maintenance OR improvement in kidney function (stabilisation or improvement in estimated glomerular filtration rate [eGFR]) Normalisation OR reduction of proteinuria to levels considered to be associated with no or little loss of kidney function over time. For example, a UK cohort study showed that achieving a urine protein:creatinine ratio less than 100mg per mmol at 1-year post diagnosis is associated with very low risk of kidney failure (Publication reference: PMID 40582408).
10. In your view, is there an unmet need for patients and healthcare professionals in C3 glomerulopathy?	Yes. There is no effective therapy for C3 glomerulopathy C3G is associated with a high rate of kidney failure C3G is associated with a high rate of disease recurrence in the kidney transplant and loss of kidney transplant function.
11. How is C3 glomerulopathy currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	C3 glomerulopathy is a kidney biopsy diagnosis So, it is treated by nephrologists and diagnosed following some indication for a kidney biopsy (proteinuria, haematuria or unexplained loss of kidney function) Once diagnosed many patients will be looked after in specialist clinics (glomerulonephritis clinics) and will be offered participation in clinical trials if appropriate. Current treatment follows KDIGO consensus guidelines (Publication references: PMID 27989322, 38844295). These will need to be changed with the advent of successful phase 3 efficacy trials of complement inhibitors: iptacopan and pegcetacoplan.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? How does healthcare resource use differ between the technology and current care?	Yes, the technology will be prescribed and managed within Kidney Clinics in Secondary Care No additional specific investment is needed as these patients are followed regularly in Secondary Care clinics and this would continue

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• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Iptacopan requires vaccination protocols that are not currently standard of care for this patient group so this would need to be part of the treatment protocol.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes There is no treatment for C3G The new technology (iptacopan) prevents complement activation, and this action is directed at the key abnormality in C3G (complement overactivation). The drug is targeting the process that we consider to be the driver of kidney damage. Consequently, we would expect that the reduction in proteinuria seen in the trials should translate to reduced rates of kidney failure
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The trials have not included individuals with C3G associated with a paraprotein and paediatric cases of C3G However, there is no reason why these groups would not respond to the therapy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology is a twice daily tablet so will not present any significant challenges The technology requires vaccination protocols (common to all complement inhibitor therapies) and a fever plan (common to all complement inhibitor therapies) No new monitoring tests are needed although there is much research ongoing to identify a clinically useful biomarker of kidney complement activation. Such a biomarker would enable us to monitor how effectively the technology is reducing or stopping kidney (glomerular) complement activation without needing kidney biopsies.

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16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting rules might match the phase 3 trial entry criteria Stopping rules would include longitudinal changes in kidney function (eGFR); longitudinal changes in urine protein loss together with consideration of the degree of acute and chronic change in the kidney biopsy and changes in complement C3 levels in the circulation.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The technology is a twice daily tablet and does not require toxicity monitoring as is required for immunosuppression used in some cases (e.g. regular blood tests to monitor for toxicity are required for patients in mycophenolate mofetil) and does not come with the significant toxicity of glucocorticoid therapy.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes, targeting the underlying pathophysiology (complement overactivation in the kidney) with iptacopan (complement factor B inhibitor) is a step change as existing treatments are supportive (blood pressure control, non-specific reduction in proteinuria using e.g. ACE inhibition, tacrolimus) or anti-inflammatory using glucocorticoids and immunosuppression (e.g. and most commonly mycophenolate mofetil).
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Like all complement inhibitors the treatment requires vaccination to reduce haemophilus, pneumococcus, meningococcus infections and requires that the patient seeks medical help promptly if develops any fever or signs of infection.
20. Do the clinical trials on the technology reflect current UK clinical practice? If not, how could the results be extrapolated to the UK setting?	Yes The primary endpoint in the phase 3 iptacopan trials was change in proteinuria at 26-weeks and this was an appropriate endpoint. Based on multiple cohort studies longitudinal proteinuria is associated with kidney failure (the higher the proteinuria the greater the risk of kidney failure).

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• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Studies have described the relationship between reduction in proteinuria overtime and future risk of kidney failure in quantitative terms, most recently a large study from the UK utilising the RADAR cohort. This showed that achieving a urine protein:creatinine ratio less than 100mg per mmol at 1-year post diagnosis is associated with very low risk of kidney failure (Publication reference: PMID 40582408). An important secondary endpoint was to determine if the treatment reduced complement activation in the kidney (glomeruli). The Iptacopan phase 3 trial data showed that glomerular complement C3 staining was reduced compared to placebo. This is a very important finding as it shows that the reduction in proteinuria was occurring in association with reduction in glomerular C3 staining. My view is that reduction in proteinuria achieved by stopping the abnormal complement activation in the kidney (as opposed to reducing proteinuria through a haemodynamic effect using blood pressure control and/or ACE inhibition alone) is, based on our understanding of the pathophysiology, more likely to protect the kidney from damage.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	The C3G APPEAR study trial excluded patients with C3G who have a paraprotein; paediatric populations (the trial recruited 12 and over) and required patients to have a low complement C3 level in circulation which many C3G patients do not have. The C3G APPEAR study also excluded transplant kidney patients although Iptacopan was studied in 11 transplant patients in separate study (Publication reference: PMID 38106570).
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	The C3G APPEAR study trial excluded paediatric populations (the trial recruited 12 and over).

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people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The use of technology that blocks C3 activation in C3G is a step change in management as it targets the underlying pathophysiology (abnormal complement activation in glomeruli).

C3G is associated with a high risk of kidney failure in both native and transplant kidneys despite the use of immunosuppression and supportive care; there is a significant unmet clinical need.

The iptacopan trial phase 3 data demonstrated a reduction in proteinuria and reduction in glomerular C3 staining and these results imply that the treatment will result in reduced rates of kidney failure.

The treatment is a twice daily tablet and appears well-tolerated.

The risk of infection common to all complement inhibition can be mitigated by pre-treatment vaccination and fever plan.

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Clinical expert statement

Iptacopan for treating complement 3 glomerulopathy [ID6283]

9 of 9

Single Technology Appraisal

Iptacopan for treating complement 3 glomerulopathy [ID6283]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with complement 3 glomerulopathy or caring for a patient with complement 3 glomerulopathy. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm on 7 July 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Part 1: Living with this condition or caring for a patient with complement 3 glomerulopathy

Table 1 About you, complement 3 (C3) glomerulopathy, current treatments and equality

1. Your name	Lewis Brimble
2. Are you (please tick all that apply)	☒ A patient with C3 glomerulopathy? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with C3 glomerulopathy? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	MPGN/DDD Support Group
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I am drawing on other's experiences (generally, not specifically) ☐ I have completed part 2 of the statement after attending the expert

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	engagement teleconference ☒ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with C3 glomerulopathy? If you are a carer (for someone with C3 glomerulopathy) please share your experience of caring for them	I first became unwell with C3G in 2010, at age nine, in the absence of any comorbidities or other past medical history. This is, unfortunately, a common age at first presentation. The disease took only two months to damage the kidneys enough for me to require dialysis. At this time, it took a considerable amount of time to receive a correct diagnosis due to knowledge of the disease being minimal, even among nephrologists. After a period of haemodialysis, I commenced peritoneal dialysis and returned home after three months in hospital, while my Mother began the work-up to donate her kidney. My clearance was not good on dialysis and I was chronically nauseated and fatigued, causing me to miss most of the remainder of primary school. After 18 months on dialysis, I received my transplant, and despite significant post-operative complications whilst still an inpatient, I returned home after four months in hospital with a healthy kidney. I was aware that the disease was recurrent, and would eventually return, however I did not expect this to happen a mere 18 months after my transplant, when my bloods were deranged at a routine follow-up appointment, and the resulting diagnostic biopsy showed some crescents on the sample. Although I was asymptomatic, it was at this point that it became clear that due to the disease and the lack of drug treatments at the time, that the clock had begun ticking, and it would only be a matter of time until I would be back on dialysis. This process took five years, during which time I was closely monitored, and was briefly treated with Eculizumab, which had some positive effects, albeit temporarily. I began taking ACE-inhibitors, and later diuretics to slow the process and manage symptoms. The process of slowly deteriorating is mentally, as well as physically, taxing. The bad memories of my previous period of dialysis were still fresh in my mind, and the inevitability of this was clear. I had dreamed of medical school, and I was preparing to sit the entrance exams and writing my application when I once more, became too

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	unwell to attend school. I recommenced dialysis a few months later, just after my 18th birthday. I was not able to sit my A levels, due to missing so much of my final year, so I left education at 18, on dialysis, and without the qualifications I'd worked so hard to achieve in order to enter medicine. This was extremely difficult for me mentally, as I knew that the competitiveness of medicine meant that that ship had most likely sailed. My second period of dialysis was haemodialysis in hospital, which gave me a better quality of life than peritoneal dialysis due to a better clearance. However, it remained very disruptive to my life, as I could only work four days a week on non-dialysis days. Some haemodialysis patients feel their worst just before a session, when the level of toxins in their bodies are highest, and some patients feel worse afterwards, due to the effects of the dialysis itself. I always felt unwell after a session, so most of the remainder of those days were spent at home with malaise, a headache or muscle cramp. During the 18 months that I spent on dialysis, while my Father was worked-up to donate his kidney, I felt extremely stuck in my situation. I could not re-enter education, go abroad, or exceed my fluid limit of 1.5l per day, at a time when I was 18 years old and trying to enjoy myself with my friends. I received my second transplant from my Dad in December 2019, at age 19. For the most part, post-operatively, I was much more straightforward this time, and began taking Iptacopan a couple of months after the surgery, remaining on it ever since. I entered the phase two study and remain on the extension study. Five and a half years on, my bloods, urine and last biopsy look very good and I hope that the treatment will continue to work for as long as the kidney does. After some time spent working in the NHS, while completing a level three qualification as a substitute for A levels, I am now two thirds through my paramedic science honours degree, and have not written off medical school yet. I know that another period of dialysis, and hopefully a transplant, is inevitable. I was extremely lucky to have two parents who were willing, and able to donate to me. However my kidney is 53 years old, so will not live forever. I hope that C3G is not the reason for this, but it is the reason that I have spent the last 15 years in and out of hospital. I have been told that another transplant may not be possible due to the

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	amount of abdominal scar tissue I have from previous surgeries, so I am very hopeful that this treatment continues to be effective. If there is one thing that I've learnt from this experience, is that serious illness can be just around the corner, and nothing is for certain, so I live my life accordingly, taking every opportunity, improving myself and helping others.
7a. What do you think of the current treatments and care available for C3 glomerulopathy on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I do not know of any other treatments specific to C3G that are currently available on the NHS. There is no cure for C3G. My use of Eculizumab was off-label. In the absence of drug treatments, the only treatments are dialysis and transplant, which do not treat the disease whatsoever, and do not prevent its recurrence.
8. If there are disadvantages for patients of current NHS treatments for C3 glomerulopathy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The lack of available drug treatments is a disadvantage in itself, as in the absence of treatment, the disease will inevitably lead to end-stage renal failure. The duration of this deterioration may differ however the inevitability remains. Dialysis provides a poor quality of life, due to the time spent receiving treatment (typically four hours, three times a week + time spent putting on/taking off from the machine + travel time if in hospital). As previously mentioned, patients may still feel unwell for long periods of time on dialysis, and be fluid and diet restricted as the machine cannot remove these things as well as a kidney would. Furthermore, long periods of dialysis are associated with a lower life expectancy. A transplant, albeit a major surgical procedure with dozens of post-operative follow-up appointments, eventually provides a far superior quality of life to dialysis, as most patients should lead a relatively normal life when transplanted. The only exception being that they are required to take lifelong immunosuppression medication, which makes them more susceptible to communicable disease. However, transplant is not a cure and does not have any effect on the disease activity. As soon as a person is transplanted, C3G is already working to damage the kidney, until it is no longer functioning.
9a. If there are advantages of iptacopan over current	Iptacopan, as the first-in-kind treatment for C3G, holds many advantages over the

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treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does iptacopan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	current treatments (none) Iptacopan is extremely easy to administer, as an oral capsule, taken twice per day. It is another form of immunosuppression, therefore more care must be taken to avoid communicable disease, however many patients with C3G would be doing this anyway due to other immunosuppressant use. Iptacopan allows the patient to avoid dialysis and live a normal life, without the emotional toll that arises from knowing that any kidney is deteriorating as a result of C3G.
10. If there are disadvantages of iptacopan over current treatments on the NHS please describe these. For example, are there any risks with iptacopan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I cannot think of any disadvantages of taking Iptacopan compared to transplant alone. The risks were clearly stated to me and I have not experienced any side effects of the treatment. As in any study, the adverse effects stated in the phase two study may be associated with the treatment, however may be coincidental.
11. Are there any groups of patients who might benefit more from iptacopan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I do not feel that patients currently on dialysis would benefit as much from Iptacopan as their kidneys are already damaged to the point that dialysis is required. Consequently, preventing further kidney damage may not be beneficial. Patients who have C3G who still have their native kidneys, and have not yet reached the point of requiring dialysis, and patients with C3G who have received a transplant, would benefit the most from Iptacopan, as they are all slowly deteriorating as the disease progresses. As the treatment is oral, I do not anticipate that patients with disabilities would affect the suitability of the treatment. Capsules would be taken in the usual way for them. The manufacturer would have to advise whether the capsule could be broken for the treatment to be given via the parental route.
12. Are there any potential equality issues that should be taken into account when considering C3 glomerulopathy and iptacopan? Please explain if you	Knowledge of the condition among nephrologists has improved in the 15 years that I have been associated with the disease. However, there are still doctors who are not aware of the condition, or any associated treatments. This differs depending on the

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think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	geographical location of the patient. Unfortunately, I have found that sometimes, many patients, including the elderly, who may not have access to the internet, are also under-informed as to the condition they have and the fact that there are potential new treatments in the pipeline. I have always been vocal about my condition with my clinicians and we encourage this among all patients with C3G, however I believe that more awareness is needed among nephrologists and patients about the disease and Iptacopan.
13. Are there any other issues that you would like the committee to consider?	N/A

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- C3G currently has no cure or effective treatments, except dialysis and transplant, which merely delay end-stage renal failure and do not target the specific mechanism of the disease.
- C3G is extremely disruptive to patient's lives, as not only will it lead to the requirement of dialysis, but the gradual deterioration is physically, mentally and emotionally difficult for patients and their families.
- Iptacopan is the first in kind treatment for C3G and has been shown to be effective.
- Iptacopan has the potential to prevent other patients from requiring dialysis, an expensive treatment that holds a low quality of life, whether they have their native kidneys or have been transplanted.
- Iptacopan is easy to administer, and causes little to no side effects.

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Erasmus School of
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Maastricht University

Iptacopan for treating complement 3 glomerulopathy [ID6283]

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Contributions of authors:

Huiqin Yang acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong also acted as project lead as well as health economist on this assessment and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Teresa Holly, Bradley Sugden, and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Xiaoyu Tian acted as systematic reviewers as well as health economists on this assessment. Huiqin Yang and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
ANCOVA	Analysis of covariance
APD	Automated peritoneal dialysis
ARB	Angiotensin II receptor blocker
ASN	American Society of Nephrology
AWMSG	All Wales Medicines Strategy Group
Bb	Cleaved Factor B
BIC	Bayesian information criterion
BSC	Best supportive care
b.i.d.	Twice daily
BM	Biomarkers
BNF	British National Formulary
C3	Complement component 3
C3G	Complement 3 glomerulopathy
C3GN	Complement 3 glomerulonephritis
C4	Complement component 4
C5b-9	Complement 5b-9 complex
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPD	Continuous ambulatory peritoneal dialysis
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CFAS	Combined full analysis set
CFHR5	Complement Factor H-related protein 5
CfB	Change from baseline
CH50	Complement haemolytic activity 50%
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CON	Confidential
CoS	Corticosteroid
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSAF	Combined safety analysis set
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
D	Day
DARE	Database of Abstracts of Reviews of Effects
DDD	Dense deposit disease
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSP	Disease Specific Programme
DSU	Decision Support Unit
EAG	External Assessment Group
ECM	Established clinical management
EED	Economic Evaluation Database
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Electronic marketing information tool
EOS	End of study
EQ-5D	European Quality of Life-5 Dimensions

EQ-5D-3L	European Quality of Life-5 Dimensions 3-Levels
EQ-5D-5L	European Quality of Life-5 Dimensions 5-Levels
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
EUCTR	European Union Clinical Trials Register
EUR	Erasmus University Rotterdam
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
HAS	Haute Autorité de santé
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
HCRU	Healthcare resource utilisation
HD	Haemodialysis
HLGT	High Level Group Terms
HRQoL	Health-related quality of life
HS	Health state
HSUV	Health state utility value
I/C	Intercurrent events
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
Incr.	Incremental
iNHB	Incremental net health benefit
IQWiG	Institute for Quality of Efficiency in Health Care
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
J2R	Jump to reference
KRT	Kidney replacement therapy
KSR	Kleijnen Systematic Reviews Ltd
LS	Least squares
LY	Life years
MA	Marketing Authorisation
MAR	Missing-at-random
MD	Mean difference
MEDLINE	Medical Literature Analysis and Retrieval System Online
mg	Milligram
MMF	Mycophenolate mofetil
MMRM	Mixed model for repeated measures
MPA	Mycophenolic acid
MPGN	Membranoproliferative glomerulonephritis
MPS	Mycophenolate sodium
MRA	Mineralocorticoid receptor antagonist
N	Total number of patients
N/A	Not applicable
NHB	Net Health Benefit
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	Netherlands
NR	Not reported
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient Access Scheme

PBAC	Pharmaceutical Benefits Advisory Committee
PD	Peritoneal dialysis
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal haemoglobinuria
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PY	Patient-years
QoL	Quality of life
QALY	Quality-adjusted life year
RaDaR	National Registry of Rare Kidney Diseases
R	Randomisation
RAS	Randomised analysis set
RAS	Renin-angiotensin system
RCT	Randomised controlled trial
ROBINS-I	Risk Of Bias In Non-randomised Studies - Intervention
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical analysis plan
SCR	Screening set
SD	Standard deviation
SE	Standard error
SGLT2i	Sodium-glucose co-transporter-2 inhibitor
SLR	Systematic literature review
SMC	Scottish Medicines Council
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System Organ Classes
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TLR	Targeted literature review
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UA	Urinary albumin
UACR	Urine albumin-to-creatinine ratio
UP	Urinary protein
UK	United Kingdom
UMC+	Maastricht University Medical Centre+
US	United States
UPCR	Urine protein-to-creatinine ratio
W	Week
WCN	World Congress of Nephrology
WHO	World Health Organization
WTP	Willingness-to-pay

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1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem (DP), Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (DP), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID6283	Summary of issue	Report Sections
1	Uncertainty as to whether the population in the DP includes those with C3G recurrence post-transplant	2.1 and 2.5
2	Uncertainty as to whether eculizumab is a comparator	2.3 and 2.5
3	Lack of evidence on the relative efficacy between iptacopan and eculizumab for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence	3.3
4	Suboptimal approach of estimating eGFR slopes	4.2.6
5	Assumption of a constant, CKD-stage independent speed of progression	4.2.6
6	Assumption of a constant treatment discontinuation rate for patients on iptacopan who have not reached kidney failure.	4.2.6
7	Assumption of a constant iptacopan treatment effect over the model time horizon while patients remained on treatment	4.2.6
8	(Face) validity of the chosen CKD stage 5+ utilities	4.2.8
9	Majority of QALYs and costs accumulated beyond the observed data	5.1
10	Lack of transparency regarding expert consultation	5.3
C3G = complement 3 glomerulopathy; CKD = chronic kidney disease; DP = decision problem; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; QALY = quality-adjusted life year		

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased time to disease progression with incremental QALYs in chronic kidney disease (CKD) stage 1-4 of 4.93 (283% of total deterministic incremental QALYs).

Overall, the technology is modelled to affect costs by:

- Increased acquisition costs (with Patient Access Scheme [PAS]) in iptacopan + standard of care (SoC) arm (increased costs of [REDACTED], [REDACTED] of the total deterministic incremental costs).

The modelling assumptions that have the greatest effect on the ICER are:

- The assumption that the iptacopan before-after comparison using APPEAR-C3G including the open-label extension study is reflective of treatment effectiveness in United Kingdom (UK) clinical practice. The upper (10.39) and lower (3.48) parameter values of the (deterministic) one-way sensitivity analysis of iptacopan treatment effectiveness resulted in ICERs of [REDACTED] and [REDACTED], respectively.

1.3 The DP: summary of the EAG's key issues

The DP addressed in the company submission (CS) is broadly in line with the Final Scope issued by NICE. However, there is a lack of evidence on a subgroup of patients (Table 1.2) as well as on certain comparators (Table 1.3).

Table 1.2: Key issue 1. Uncertainty as to whether the population in the DP includes those with C3G recurrence post-transplant and the potential lack of comparative evidence in this subgroup

Report Sections	2.1 and 2.5
Description of issue and why the EAG has identified it as important	There is a lack of clarity in the population eligible for iptacopan, specifically as to whether the post-transplant C3G recurrence subgroup should be included.
What alternative approach has the EAG suggested?	The company stated in the CS that: "...the trial was single-arm and the sample size was considered too small (N=11) to robustly inform economic modelling in a post-transplant subgroup. Therefore, the economic analyses presented are based on data in native kidney patients. Given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients." This would imply that the C3G recurrence post-transplant subgroup is included in the DP population even if there are no comparative data to inform clinical effectiveness in this subgroup. It is also unclear what the comparator would be for this subgroup.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Despite any data limitations, subgroup analysis for the post-transplant recurrence of C3G could still be useful. Otherwise, this subgroup could be excluded from the DP.
C3G = complement 3 glomerulopathy; DP = decision problem; EAG = External Assessment Group; NICE = National Institute for Health and Care Excellence; UK = United Kingdom	

Table 1.3: Key issue 2. Uncertainty as to whether eculizumab is a comparator

Report Sections	2.3 and 2.5
Description of issue and why the EAG has identified it as important	Eculizumab was excluded as a comparator in clinical effectiveness analyses and a CEA in the DP.
What alternative approach has the EAG suggested?	The company were asked to include eculizumab for comparison with iptacopan in the appropriate subgroup as used in UK clinical practice or exclude this subgroup from the DP. The company responded that there is no head-to-head data for iptacopan, and an ITC is deemed infeasible due to limited data (small trials, which lack comparability with the iptacopan trials). They went on to argue that eculizumab use is extremely limited in UK clinical practice (~1 patient per year on average) and that eculizumab is of reduced relevance in light of the fact that iptacopan would be delivered at an earlier point in the care pathway given that NHS England criteria require evidence of a significant decline of transplant function (>20% decline in eGFR) within the previous 3 months before eculizumab can be initiated. This might indicate that, if recurrent C3G post-transplant patients were treated with iptacopan then they would never become eligible for eculizumab, which would rule it out as a comparator.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Demonstration that iptacopan is cost-effective in the post-transplant C3G recurrence population, and that no patients would then be eligible for eculizumab might remove the need for a comparison. Otherwise, a comparison with eculizumab would still be needed, but the limited data might preclude any formal comparison (see Key issue 3).
C3G = complement 3 glomerulopathy; CEA = cost-effectiveness analysis; DP = decision problem; EAG = External Assessment Group; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ITC = indirect treatment comparison; NHS = National Health Service; UK = United Kingdom	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

A full summary of the clinical effectiveness evidence conclusions can be found in Section 3.5 of this report. The key issue of clinical effectiveness evidence was that there was a lack of evidence on the relative efficacy between iptacopan and eculizumab for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive complement 3 glomerulopathy (C3G) recurrence (see Table 1.4).

Table 1.4: Key issue 3. Lack of evidence on the relative efficacy between iptacopan and eculizumab for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence

Report Section	3.3
Description of issue and why the EAG has identified it as important	The company stated in the evidence submission that ITC analysis for the comparison of iptacopan versus eculizumab was not feasible because the outcome (eGFR) used in the economic model was not reported in the eculizumab trials. Therefore, the EAG asked the company to conduct ITC analyses based on other outcomes (e.g.

Report Section	3.3
	proteinuria) that were reported in the eculizumab trials for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence, with the use of the post-transplant recurrent cohort of the Phase 2 trial of iptacopan. In responding to the EAG's request, the company stated that an ITC of proteinuria outcomes was not considered meaningful due to marked differences in the eculizumab trial populations and the patients included in the post-transplant recurrent cohort of the iptacopan Phase 2 trial. The EAG agreed that given the substantial differences of proteinuria levels at baseline between the included patients from the three eculizumab trials and the patients included in the post-transplant recurrent cohort of the iptacopan Phase 2 trial, it would be less meaningful to conduct an ITC based on proteinuria outcomes from these trials. Given that an ITC analysis for the comparison of iptacopan versus eculizumab was not conducted, the EAG considered that there was a lack of evidence on the relative efficacy between iptacopan and eculizumab for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence.
What alternative approach has the EAG suggested?	Given that eculizumab was used in UK clinical practice for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence as specified in the NICE scope, the company should ideally conduct an ITC to assess the relative efficacy between iptacopan and eculizumab for this subgroup where possible. The EAG acknowledged the limitations in the data.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that the company should ideally conduct an ITC to assess the relative efficacy between iptacopan and eculizumab for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence where possible. The EAG acknowledged the limitations in the data. If the ITC for this subgroup was not conducted, the company should exclude eculizumab as a comparator from the DP.
C3G = complement 3 glomerulopathy; DP = decision problem; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; UK = United Kingdom	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the Tables below.

Table 1.5: Key issue 4. Data used to generate eGFR slopes

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company estimated eGFR slopes using a before-after comparison based on APPEAR-C3G, including the open-label extension study. This approach is considered suboptimal by the EAG as the resulting iptacopan treatment effect was based on an observational comparison rather than a randomised comparison and is therefore prone to bias.
What alternative approach has the EAG suggested?	The EAG requested analyses: 1) use RaDaR data to inform SoC and apply the iptacopan treatment effect based on the randomised comparison from APPEAR-C3G to inform the iptacopan; and 2) use pre-iptacopan data from APPEAR-C3G to inform SoC and apply the iptacopan treatment effect based on the randomised comparison from APPEAR-C3G to inform the iptacopan.
What is the expected effect on the cost effectiveness estimates?	Both analyses increased the ICER to £[REDACTED] and £[REDACTED] respectively.
What additional evidence or analyses might help to resolve this key issue?	N/A
EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; ICER = incremental cost-effectiveness ratio; N/A= not applicable; RaDaR = National Registry of Rare Kidney Diseases; SoC = standard of care	

Table 1.6: Key issue 5. Assumption of a constant, CKD-stage independent speed of progression

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG questions the company's assumption that the speed of eGFR progression in the economic model was independent of CKD stage and constant over the modelled time horizon.
What alternative approach has the EAG suggested?	The EAG requested analyses: 1) using CKD stage-dependent eGFR decline rates from the iptacopan trials in C3G; and 2) using time-dependent eGFR decline rates from the iptacopan trials in C3G.
What is the expected effect on the cost effectiveness estimates?	The above-mentioned analyses requested by the EAG were not implemented by the company in their economic model. Over- or underestimation of the speed at which patients' eGFR declines in the economic model is likely to have significant implications for the long-term modelling of costs and effects, particularly those associated with KRT such as dialysis and kidney transplantation.
What additional evidence or analyses might help to resolve this key issue?	Analyses using CKD stage-dependent and time-dependent eGFR decline rates as requested above, potentially informed by other literature/external data if not deemed feasible based on APPEAR-C3G.
CKD = chronic kidney disease; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; KRT = kidney replacement therapy	

Table 1.7: Key issue 6. Modelling of treatment discontinuation

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG questions the assumption of a constant treatment discontinuation rate of 0.063 per year for patients on iptacopan who have not reached kidney failure.
What alternative approach has the EAG suggested?	The EAG requested analyses: 1) exploring alternative, time-varying discontinuation rates informed by external data, expert inputs and/or other TAs in CKD; and 2) exploring TTD analyses for both the pooled data and for the APPEAR-C3G trial only consistent with NICE DSU TSD 14.
What is the expected effect on the cost effectiveness estimates?	Using the exponential and log-normal curves from the TTD analyses led to a minor decrease in the ICER. The impact of TTD analyses may be more pronounced when combined with assumptions related to waning of the iptacopan treatment effect.
What additional evidence or analyses might help to resolve this key issue?	The company should provide full details of the TTD model selection process based on the NICE DSU TSD 14 guidance for the EAG to assess the most appropriate curve to inform treatment discontinuation in the economic model.
CKD = chronic kidney disease; DSU = Decision Support Unit; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; TA = Technology Appraisal; TSD = Technical Support Document; TTD = time to treatment discontinuation	

Table 1.8: Key issue 7. Assumption of a constant iptacopan treatment effect over the model time horizon while patients remained on treatment

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG considers the assumption of a constant iptacopan treatment effect over the model time horizon while patients remained on treatment to be insufficiently assessed and justified.
What alternative approach has the EAG suggested?	The EAG requested further justification and analyses to assess the assumption of a constant treatment effect during the observed period (e.g. tabulated time-to-event data, Kaplan-Meier plots, cumulative hazard plots), as well as scenario analyses exploring treatment waning beyond the observed period.
What is the expected effect on the cost effectiveness estimates?	The analyses requested by the EAG were not implemented by the company in their economic model. Introducing waning of treatment effect would generally reduce the long-term benefit of the intervention and as a result increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	Analyses to assess the assumption of a constant treatment effect during the observed and beyond the observed period as requested above.
EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.9: Key issue 8. (Face) validity of the chosen CKD stage 5+ utilities

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The EAG questions the relatively low literature-based CKD stage 5+ utility values, potentially resulting from age-related comorbidities in the older, wider CKD population in the study by Lee 2005 as compared to the modelled C3G population.

Report Section	4.2.8
What alternative approach has the EAG suggested?	The EAG has suggested alternatively the use of Liem 2008 utility values, and Sinha 2025 utility values for cross validation. It further requested a more detailed overview of relevant TAs to cross-validate utilities.
What is the expected effect on the cost effectiveness estimates?	Higher CKD 5+ stage utilities will increase the ICER, as shown by the scenario analysis using the post-transplant value (0.81) from Liem 2008 (ICER substantially increased by £[REDACTED]).
What additional evidence or analyses might help to resolve this key issue?	Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients might help to resolve this key issue.
C3G = complement 3 glomerulopathy; CKD = chronic kidney disease; EAG = External Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; ICER = incremental cost-effectiveness ratio; TA = Technology Appraisal	

Table 1.10: Key issue 9. Majority of QALYs and costs accumulated beyond the observed data

Report Section	5.1
Description of issue and why the EAG has identified it as important	The majority of absolute and incremental QALYs and costs for iptacopan + SoC and SoC were accumulated beyond the observed data period. Moreover, the proportion of costs accumulated beyond the observed data for SoC was substantially larger than for iptacopan + SoC.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Additional explanation as to the mechanism by which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence.
EAG = External Assessment Group; QALY = quality-adjusted life year; SoC = standard of care	

Table 1.11: Key issue 10. Lack of transparency regarding expert consultation

Report Section	5.3
Description of issue and why the EAG has identified it as important	Various modelling assumptions in the CS were justified based on expert opinion from advisory board meetings and consultations. The EAG had no access to the full minutes of these advisory board meetings.
What alternative approach has the EAG suggested?	The EAG requested access to the full meeting minutes in clarification question B23, but did not receive these.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses	Provide the full advisory board meeting minutes.

Report Section	5.3
might help to resolve this key issue?	
CS = company submission; EAG = External Assessment Group	

1.6 Summary of the EAG's view

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was £[REDACTED] per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [REDACTED]% at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustment was estimating the estimated glomerular filtration (eGFR) slope for SoC based on National Registry of Rare Kidney Diseases (RaDaR) data and subsequently applying the iptacopan treatment effect from the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope. The EAG's ICER increased most in the scenario analysis with alternative assumptions regarding kidney replacement therapy (KRT) utilities.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of iptacopan + SoC, which can be partly resolved by the company. This includes providing CKD stage-dependent and time-dependent eGFR decline rates, full details of the time to treatment discontinuation (TTD) model selection process based on the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance, analyses to assess the assumption of a constant treatment effect during and beyond the observed period, analyses of additional (patient-level) European Quality of Life-5 Dimensions (EQ-5D) data on CKD stage 5+ patients, explanation and justification of the mechanisms by which the economic model generated a substantial proportion of QALYs and costs beyond the observed data, and providing the full advisory board meeting minutes. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of iptacopan + SoC compared with SoC.

Table 1.12: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Deterministic							
CS base-case							
SoC	£355,162	15.13	-	-	-	-	-
Iptacopan + SoC	[REDACTED]	16.88	[REDACTED]	1.74	[REDACTED]	[REDACTED]	[REDACTED]
Fixing error (1 - [probabilistic analyses only] include CKD stage 1-4 utilities in PSA)							
Fixing violation (2 - per pack costing approach for iptacopan and SoC therapies)							
SoC	£355,192	15.13	-	-	-	-	-
Iptacopan + SoC	[REDACTED]	16.88	[REDACTED]	1.74	[REDACTED]	[REDACTED]	[REDACTED]
Matter of Judgement (3 - population baseline characteristics from RaDaR)							
SoC	£390,532	14.57	-	-	-	-	-
Iptacopan + SoC	[REDACTED]	16.23	[REDACTED]	1.66	[REDACTED]	[REDACTED]	[REDACTED]

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Matter of Judgement (4 - eGFR slope based on RaDaR for SoC, apply double blind treatment effect for iptacopan)							
SoC	£288,267	15.70	-	-	-	-	-
Iptacopan + SoC	████████	16.86	████████	1.16	████████	██████	██████
Matter of Judgement (5 - all grade 3+ AEs from controlled safety set)							
SoC	£359,350	15.11	-	-	-	-	-
Iptacopan + SoC	████████	16.85	████████	1.74	████████	██████	██████
EAG base-case							
SoC	£292,470	15.68	-	-	-	-	-
Iptacopan + SoC	████████	16.84	████████	1.16	████████	██████	██████
Probabilistic							
CS base-case							
SoC	£355,352	15.15	-	-	-	-	-
Iptacopan + SoC	████████	16.69	████████	1.54	████████	██████	██████
Fixing errors (1 - [probabilistic analyses only] include CKD stage 1-4 utilities in PSA)							
SoC	£355,352	15.15	-	-	-	-	-
Iptacopan + SoC	████████	16.69	████████	1.54	████████	██████	██████
Fixing violation (2 - per pack costing approach for iptacopan and SoC therapies)							
SoC	£355,382	15.15	-	-	-	-	-
Iptacopan + SoC	████████	16.69	████████	1.54	████████	██████	██████
Matter of Judgement (3 - population baseline characteristics from RaDaR)							
SoC	£391,534	14.58	-	-	-	-	-
Iptacopan + SoC	████████	16.05	████████	1.47	████████	██████	██████
Matter of Judgement (4 - eGFR slope based on RaDaR for SoC, apply double blind treatment effect for iptacopan)							
SoC	£292,779	15.65	-	-	-	-	-
Iptacopan + SoC	████████	16.82	████████	1.17	████████	██████	██████
Matter of Judgement (5 - all grade 3+ AEs from controlled safety set)							
SoC	£359,524	15.13	-	-	-	-	-
Iptacopan + SoC	████████	16.67	████████	1.54	████████	██████	██████
EAG base-case							
SoC	£296,967	15.63	-	-	-	-	-

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Iptacopan + SoC	████████	16.80	████████	1.17	████████	██████	██████
AE = adverse event; CKD = chronic kidney disease; CS = company submission; EAG = External Assessment Group; eGFR = epidermal growth factor receptor; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = Net Health Benefit; PSA = probabilistic sensitivity analysis; QALY = quality adjusted life year; RaDaR = National Registry of Rare Kidney Diseases; SoC = standard of care							

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
Population	Adults with C3G	Adults with C3G	In line with the final scope. The DP reflects the currently available evidence and expected licensed population. A clinical trial for iptacopan in adolescents with C3G (12 to below 18 years of age) is currently ongoing, and a licence extension to adolescents will be pursued at a later date subject to the trial read-out.	There is some uncertainty as to the precise point in the care pathway and whether C3G recurrence post-transplant is included.
Intervention	Iptacopan	Iptacopan	In line with the final scope. This submission considers iptacopan 200 mg b.i.d. in combination with ECM, comprising of ACEis/ARBs (unless not tolerated or contraindicated), with some patients also being on CoS, MMF and/or SGLT2is. This aligns with the design of the iptacopan clinical trials, in which patients were administered iptacopan on top of these background therapies.	In line with the NICE scope.
Comparator(s)	ECM without iptacopan, which may include: - ACEis - ARBs	ECM without iptacopan, which may include: - ACEis - ARBs	ECM is considered as comparator in line with the final scope. A comparison with eculizumab was not undertaken due to	There is some uncertainty as to whether eculizumab is a comparator and therefore whether comparative

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
	- CoS - MMF - SGLT2is In people who have previously had a kidney transplant and who have highly aggressive C3G recurrence as specified in the NHS England clinical commissioning policy for eculizumab: - eculizumab	- CoS - MMF - SGLT2is	limitations of the evidence base. However, eculizumab is considered of limited relevance as a comparator for this submission, for the following reasons: Use in UK clinical practice is uncommon. With the NHS England commissioning policy restricting use to a small subgroup among patients with post-transplant recurrence, on average only one person per year was able to access eculizumab as a treatment for C3G since the commissioning policy was put in place in 2017. The use of eculizumab is limited to patients with highly aggressive recurrent disease. Amongst others, the criteria require evidence of a significant decline of transplant function (>20% decline in eGFR) within the previous 3 months. Treatment with iptacopan, on the other hand, can be started as soon as recurrence is diagnosed via biopsy of the transplanted kidney, before the onset of clinical signs such as eGFR decline; this is in line with the available clinical trial evidence and the draft SmPC (Section 4.2). As such, UK clinicians have advised that they	evidence should be presented, albeit of low quality.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
			would want to start iptacopan at an earlier point of disease recurrence than eculizumab, which further reduces the relevance of eculizumab as a comparator for the intended positioning of iptacopan.	
Outcomes	The outcome measures to be considered include: - Kidney function (for example, eGFR) - Proteinuria - Disease progression (need for kidney transplant and/or dialysis) - Mortality - Adverse effects of treatment - HRQoL	The outcome measures presented in this submission include: - Kidney function (eGFR) - Proteinuria (CfB in UPCR) - Disease progression (dialysis and/or transplant) - Mortality - Adverse effects of treatment - HRQoL	Data for these outcomes are presented in this submission to the extent to which they are available. Data for progression to dialysis/transplant as well as mortality data are limited due to the follow-up duration of the iptacopan clinical trials.	In line with the NICE scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	The economic modelling approach presented in this submission is in line with the reference case.	The cost of kidney biopsy was not modelled in this submission as patients are biopsied to obtain a diagnosis of C3G, irrespective of the existence of iptacopan, and no additional biopsy is required to establish eligibility for iptacopan, as confirmed by UK clinical expert opinion. Therefore, based on expert advice, costs associated with diagnostic testing have not been included.	No comment.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
	Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of iptacopan is conditional on the results of renal biopsy. The economic modelling should include the costs associated with diagnostic testing in people who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.			
Subgroups to be considered	If evidence allows, the following subgroups will be considered: - People who have and have not had a kidney transplant - People with C3GN - People with DDD - People with CFHR5 nephropathy	Clinical evidence is presented for the efficacy and safety of iptacopan in patients who have not had a kidney transplant (native kidney patients) and in patients who had disease recurrence following a kidney transplantation (post-transplant recurrent patients). Economic modelling is based on data in native kidney patients.	The randomised, placebo-controlled iptacopan Phase 3 trial APPEAR-C3G included patients with native kidney disease. While the Phase 2 trial included a cohort of patients with post-transplant recurrence of C3G, the trial was single-arm, and the sample size was considered too small (N=11) to robustly inform economic modelling in a post-transplant subgroup. Therefore, the economic analyses presented are based on data in native kidney patients. Given that the underlying disease mechanism is the same in native	No comparative evidence has been presented to demonstrate the effectiveness of iptacopan in the C3G recurrence post-transplant subgroup or the small subgroup of those eligible for eculizumab (>20% decline in eGFR) within the previous 3 months).

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
			kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients. Furthermore, the approach to model only a native kidney population aligns with that taken in previous NICE appraisals in other CKDs, with the NICE recommendations for these treatments not excluding transplanted patients even where transplanted patients were excluded from the clinical trials. This submission does not present subgroup analyses for people with C3GN and DDD apart from a subgroup analysis of the primary endpoint of APPEAR-C3G, where interpretability of results is limited by the small sample size and imbalance between groups (DDD patients in iptacopan arm n=9, placebo arm n=1). Whilst a distinction between C3GN and DDD is made based on kidney tissue biopsy findings, the clinical presentation, disease course, and management of these C3G subtypes are generally considered	

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
			to be consistent. Consequently, the clinical and cost effectiveness of iptacopan are not expected to differ between people with C3GN and DDD. Similarly, CFHR5 nephropathy is a subtype of C3GN, caused by a genetic mutation endemic to people of Cypriot origin, and clinical and cost effectiveness of iptacopan are not expected to differ from other people with C3G.	
Special considerations including issues related to equity or equality	Equality impact assessment – Scoping: <i>Potential equality issues identified during the scoping process</i> Children (under 12 years of age) are excluded from the licence. Furthermore, the company indicated that its submission will exclude young people (under 18 years of age). Consultees noted that access for people of all ages should be considered. There is a longer waiting time for kidney transplants for Black people and people with an Asian family background compared to White people. A third of people (35%) waiting for a kidney across the UK are from minority ethnic groups but in 2017/18, of those	Novartis supports access to treatment for all people with C3G regardless of their age and ethnicity. While the currently available iptacopan clinical trial results and expected licensed indication are limited to adults, Novartis is committed to pursuing a licence extension and access to iptacopan for younger people with C3G as soon as the available evidence permits. The iptacopan clinical trials in C3G enrolled patients globally, including in the UK. In the APPEAR-C3G study,	N/A	

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
	providing their ethnicity when registering on the NHS Organ Donor Register, only 3.3% had an Asian family background, 1% were Black and 2% were mixed race. <i>Preliminary view as to what extent these potential equality issues need addressing by the Committee</i> The committee should consider iptacopan within its MA (adult population), however the committee may consider whether Commissioning Medicines for Children in Specialised Services applies in this instance. The committee should consider whether the longer waiting times faced by Black people and people of Asian family backgrounds represents a health inequality, and if so the impact of guidance on this inequality.	24.3% of participants were of Asian ethnicity and 2.7% were of Black or African American ethnicity.		
Based on Table 1 of CS¹ ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; b.i.d. = twice daily; C3G = complement 3 glomerulopathy; C3GN = complement 3 glomerulonephritis; CfB = change from baseline; CFHR5 = complement Factor H-related protein 5; CoS = corticosteroids; CS = company submission; DDD = dense deposit disease; DP = decision problem; EAG = External Assessment Group; ECM = established clinical management; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; MA = Marketing Authorisation = milligram; MMF = mycophenolate mofetil; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SmPC = summary of product characteristics; UK = United Kingdom; UPCR = urine protein-to-creatinine ratio				

2.1 Population

The population in the decision problem (DP) is the same as in the National Institute for Health and Care Excellence (NICE) scope i.e. adults with complement 3 glomerulopathy (C3G).^{1, 2}

In fact, the proposed positioning of iptacopan is shown in Figure 5 of the company submission (CS) and stated to be: “...in patients who remain at risk of disease progression.” No other description of the population is provided.

EAG comment: There is a lack of clarity in the population eligible for iptacopan. In response to the request for subgroup analysis in the NICE scope, the company state: “While the Phase 2 trial included a cohort of patients with post-transplant recurrence of C3G, the trial was single-arm and the sample size was considered too small (N=11) to robustly inform economic modelling in a post-transplant subgroup. Therefore, the economic analyses presented are based on data in native kidney patients. Given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients.” (see Table 2.1). This would imply that the C3G recurrence post-transplant subgroup is included in the DP population even if there is no subgroup analysis.

In conclusion, it appears that the DP population includes both native and post-transplant C3G recurrence, although this is unclear and therefore can be regarded as a key issue. It also raises the questions as to the appropriate comparator for this subgroup.

2.2 Intervention

The intervention in the DP is the same as in the NICE scope i.e. iptacopan, given as 200 mg twice daily (b.i.d.) in combination with established clinical management (ECM), comprising of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEis/ARBs) (unless not tolerated or contraindicated), with some patients also being on corticosteroids (CoS), mycophenolate mofetil (MMF) and/or sodium-glucose co-transporter-2 inhibitor (SGLT2is).^{1, 2} This aligns with the design of the iptacopan clinical trials, in which patients were administered iptacopan on top of these background therapies.

2.3 Comparators

The comparators in the NICE scope are:

- ECM without iptacopan, which may include:
 - ACEis
 - ARBs
 - CoS
 - MMF
 - SGLT2is
- In people who have previously had a kidney transplant and who have highly aggressive C3G recurrence as specified in the NHS England clinical commissioning policy for eculizumab:
 - Eculizumab

However, DP excludes eculizumab on the basis that it is considered of limited relevance as a comparator because in United Kingdom (UK) clinical practice its use is uncommon, with the National Health

Service (NHS) England commissioning policy restricting use to a small subgroup among patients with post-transplant recurrence, and its use is limited to patients with highly aggressive recurrent disease.

EAG comment: Therefore, in the clarification letter the company were asked to include eculizumab as a comparator in clinical effectiveness analyses and a cost-effectiveness analysis (CEA) for the appropriate subgroup as used in UK clinical practice, or exclude this subgroup from the DP.³ The company responded:⁴ *“There is no head-to-head data for iptacopan versus eculizumab in C3G, and, as further explained in the response to clarification question A11, an indirect treatment comparison is deemed infeasible. It was therefore not possible to include eculizumab as a comparator within the cost-effectiveness model.”*

They went on to argue that eculizumab use is extremely limited in UK clinical practice (~1 patient per year on average) and is of reduced relevance in light of the fact that iptacopan would be delivered at an earlier point in the care pathway given that NHS England criteria require evidence of a significant decline of transplant function (>20% decline in estimated glomerular filtration rate [eGFR]) within the previous 3 months before eculizumab can be initiated, in contrast with iptacopan, which: *“...can be started as soon as recurrence is diagnosed via biopsy of the transplanted kidney, and before the onset of clinical signs such as eGFR decline. this is in line with the available clinical trial evidence from the iptacopan Phase 2 study (see CS Section 2.5.1) and the draft SmPC (section 4.2).”* This might indicate that, if recurrent C3G post-transplant patients were treated with iptacopan then they would never become eligible for eculizumab, which would rule it out as a comparator. However, this can only be the case if iptacopan is found to be cost effective and recommended at this earlier point in the care pathway. This uncertainty implies a key issue, notwithstanding the uncertainty in the DP population described above.

2.4 Outcomes

The outcomes in the DP are in line with those in the NICE scope.

2.5 Subgroup analyses

The company did not perform any of the subgroup analyses specified in the NICE scope. In particular, they stated that the only trial data to inform those patients with C3G recurrence post-transplant was from the very small single arm Phase 2 trial, and that the mechanism of action of iptacopan would imply the generalisability from the APPEAR trial, which was in the native population.¹ However, an indirect treatment comparison (ITC) could have been performed, albeit with much uncertainty given the small sample size. Therefore, the lack of subgroup analysis for this population is a key issue.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The company performed a systematic literature review (SLR) to identify and summarise the available randomised controlled trial (RCT) and other relevant evidence relating to the efficacy and safety of iptacopan and other interventions for the treatment of adults with C3G.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.¹ Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health [CADTH]) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.⁵ The EAG has presented only the major limitations of each search strategy in the report.

Appendix B of the CS details the SLR conducted to identify published evidence on the clinical efficacy and safety of iptacopan and any potentially relevant comparators in the treatment of C3G.⁶

EAG comment:

- Searches were undertaken to identify published evidence on the clinical efficacy and safety of iptacopan and any potentially relevant comparators in the treatment of C3G. The CS, Appendix B and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 4, 6}
- The following databases were searched from inception on 3 October 2021 and updated on 14 October 2024: Embase, MEDLINE, the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL).
- Three key conference proceedings (European Renal Association - European Dialysis and Transplant Association [ERA-EDTA], the American Society of Nephrology [ASN] and the World Congress of Nephrology [WCN]) were searched on 16 December 2021 and updated on 18-22 October 2024.
- The following trials registries were searched on 16 November 2021 and updated on 22 October 2024: www.ClinicalTrials.gov, the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) and the European Union Clinical Trials Register (EUCTR).
- Ten regulatory and Health Technology Assessment (HTA) bodies' websites, the Database of Abstracts of Reviews of Effects (DARE), the NHS Economic Evaluation Database (NHS EED) and the HTA database were searched in October 2024. Bibliographies of systematic reviews and meta-analyses and other selected studies were reference checked. Supplementary searches were conducted on Google and Google Scholar.
- No date or language limits were applied to the searches.
- The database searches for the clinical effectiveness SLR consisted of a single search facet for C3G. In the MEDLINE and Embase searches this was then combined with study design filters designed to limit results to controlled trials and non-randomised clinical trials. This broader approach to the search strategy design ensured that no relevant records were likely to be missed, as no intervention/comparator search facet was included to potentially limit the results.
- All searches were transparent and reproducible, and contained a good range of search terms, synonyms and subject headings.

3.1.2 Inclusion criteria

The company provided details on their eligibility criteria in Appendix B of the CS.¹ It is apparent that this represents a broad criteria going so far as to being vague. The Table includes the same entry for intervention and comparator and describes outcomes as '*including but not limited to*'. This Table should be clear, should be specific and should eliminate or minimise ambiguity as to be able to determine precisely what the company are looking to include but this is not the case here.

Table 3.1: Eligibility criteria in the original SLR and SLR update

	Inclusion	Exclusion
Population	Patients diagnosed with C3G Studies including patients classified as MPGN type II (now referred to as DDD) were also included.	Any other patient population. Studies conducted in mixed patient population without reporting C3G-specific data.
Interventions	Any intervention for C3G (including BSC) or placebo.	N/A
Comparator	Any intervention for C3G (including BSC) or placebo.	N/A
Outcome	Efficacy (e.g. changes in UPCR, proteinuria, serum albumin, creatinine, creatinine clearance, urine albumin creatinine ratio, eGFR, eGFR stabilisation, complement levels (C3, C4, CH50, C5b-9), C3G histological score for disease, haematuria; mortality; time to kidney failure). Safety (AEs, severe infections). Treatment discontinuation.	Studies not reporting any relevant outcomes of interest.
Study design	RCTs and non-randomised clinical trials (e.g. single arm).	Case reports, case-series, observational/real-world studies, editorials, letters, protocols, opinion papers, commentaries, news, narrative and systematic reviews ^a , non-human and in vitro studies.
Language	No restriction	N/A
Country	No restriction	N/A
Publication date	No restriction	N/A
Based on Table 7, Appendix B CS ⁶ ^a Relevant systematic reviews were considered for bibliography search. AE = adverse event; BSC = best supportive care; C3 = complement component 3; C3G = complement 3 glomerulopathy; C4 = complement component 4; C5b-9 = complement 5b-9 complex; CH50 = complement haemolytic activity 50%; DDD = dense deposit disease; eGFR = estimated glomerular filtration rate; MPGN = membranoproliferative glomerulonephritis; N/A: not applicable; RCTs = randomised controlled trials; UPCR = urine protein-to-creatinine ratio		

3.1.3 Critique of data screening and extraction

The CS states that study selection occurred in two stages: titles and abstracts were reviewed then full texts of potentially relevant articles were screened in order to obtain the final list of included studies.

Each record was screened by two independent reviewers, with any discrepancies between reviewers reconciled with the help of a third independent reviewer, at both abstract and full-text searching stage.

The EAG acknowledges that this method of screening is optimal to minimise risks of bias and error. However, the CS states that for data extraction, one reviewer performed the task, with a second reviewer being involved to conduct checks. This is a well-used method, however, it increases the likelihood of errors and bias and so the preferred method would have been used for screening, with two independent reviewers. The EAG asked the company to confirm how disagreements between the reviewer and the checker were resolved. In their response to clarification the company stated that *‘any discrepancies in data extraction were discussed between the two reviewers. If consensus could not be reached, a third independent reviewer was consulted to make a final decision’*.⁴

EAG comment: The EAG is satisfied that screening and data extraction was conducted with an appropriate method to minimise bias and error. We do of course highlight that this was not the optimal method and always recommend that such tasks are completed in duplicate independently.

3.1.4 *Quality assessment*

The APPEAR-C3G trial was assessed using the Cochrane Risk of Bias 2 tool (see Table 3.2), while the single-arm Phase 2 trial was assessed using the Cochrane Risk Of Bias In Non-randomised Studies – Intervention (ROBINS-I) tool (see Table 3.3). APPEAR-C3G was determined to be at low risk of bias, while the Phase 2 trial was considered to be associated with a moderate risk of bias.

Quality appraisals were conducted by one reviewer and then checked by another. As with screening and data extraction, this represents a widely used method but one that has an increased risk of bias and error compared to appraisals conducted independently by two reviewers. We asked the company to clarify how disagreements between reviewers were resolved. In their response to clarification the company stated that *‘any discrepancies in data extraction were discussed between the two reviewers. If consensus could not be reached, a third independent reviewer was consulted to make a final decision’*.⁴

Table 3.2: Quality assessment of included RCTs using the Risk of Bias 2 tool

Study ID	Bias arising from the randomisation process (allocation sequence generation, allocation sequence concealment)	Bias due to deviations from intended interventions (assignment to interventions as per protocol, blinding of participants, carers and trial personnel, use of appropriate analyses methods)	Bias due to missing outcome data (reasons for missing outcome data, use of appropriate imputation procedures)	Bias in measurement of the outcome (appropriate measurement methods, blinding of outcome assessor)	Bias in selection of the reported result (selective outcome data reporting)	Overall risk of bias
Cattran 1985	Some concerns	High risk	Low risk	Some concerns	Low risk	High
Tarshish 1992	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Nester 2023	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Bomback 2024 (ACCOLADE)	Low risk	Low risk	Low risk	Low risk	Low risk	Low
Nester 2024 (APPEAR-C3G)	Low risk	Low risk	Low risk	Low risk	Low risk	Low
Adapted from Table 12, Appendix B, CS ⁶ C3G = complement 3 glomerulopathy; CS = company submission; RCT = randomised controlled trial						

Table 3.3: Quality assessment of included non-randomised clinical trials using the ROBINS-I tool

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Faedda 1994	No information	Low risk	Moderate risk	Low risk	Moderate risk	No information	No information	No information

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Bomback 2012	No information	Low risk	Moderate risk	Low risk	Moderate risk	No information	No information	No information
Kocinsky 2018	No information	Low risk	Moderate risk	Low risk	Moderate risk	No information	No information	No information
Dirim 2019	No information	Low risk	Moderate risk	Low risk	Moderate risk	No information	No information	No information
Ruggenenti 2019 (EAGLE)	No information	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
Zand 2021	Moderate risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
RENEW (NCT05162066)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
Dixon 2023 (DISCOVERY)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
Wong 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
Gupta 2023	No information	Low risk	Moderate risk	No information	Moderate risk	No information	No information	No information

Adapted from Table 13, Appendix B, CS⁶

CS = company submission; ROBINS-I = Risk Of Bias In Non-randomised Studies - Intervention

EAG comment: The EAG considers that the quality appraisals were conducted with a widely used method of one reviewer with data being checked by a second. While this is not the optimal method and has higher risk of bias and error than duplicate appraisals conducted independently the EAG has looked at the relevant studies and has no major disagreements with the appraisal provided.

3.1.5 Evidence synthesis

An ITC was not conducted to determine the relative efficacy between iptacopan and relevant comparators. Details and EAG's comments are provided in Sections 3.3 for the ITC.

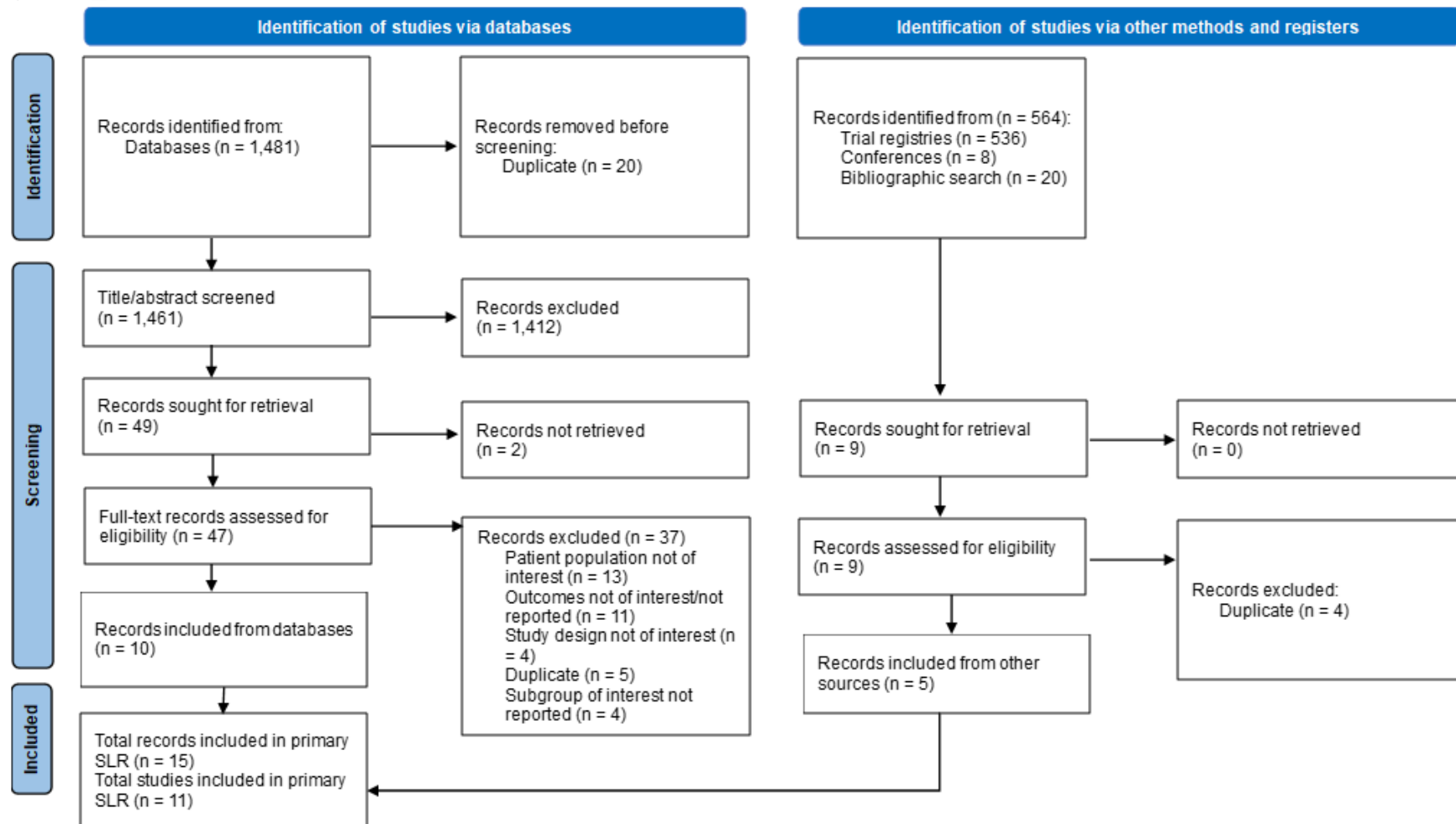
3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

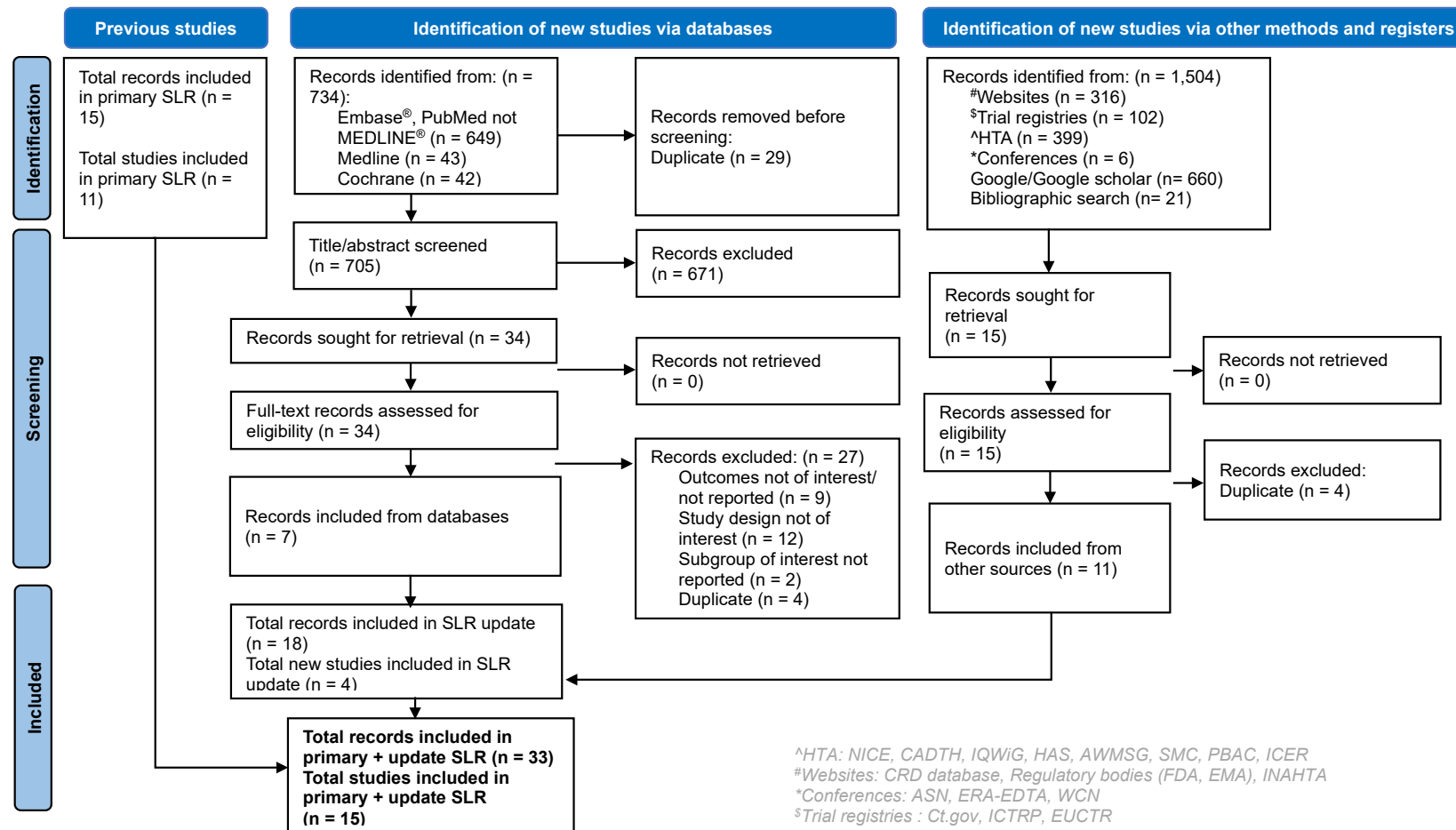
The CS reports that a SLR was conducted in October–December 2021 and updated in October 2024. The company acknowledges the SLR scope was broad, including randomised and non-randomised clinical trials in patients diagnosed with C3G, in receipt of any intervention for C3G.¹

One thousand, four hundred and eighty-one citations were identified in the database searches resulting in 1,461 citations for title and abstract screening after the removal of duplicates. Forty-nine citations were identified for the full-text review. Of these, 10 records were included. Grey literature searches identified five relevant records. Of these 15 included records, four were each linked to another publication resulting in 11 unique studies (see Figure 3.1). Seven hundred and thirty-four citations were identified in the SLR update. Seven hundred and five citations were title and abstract screened after duplicate removal. Of these, 34 citations were identified for the full-text review. Seven records were included. Grey literature searches identified 11 relevant records. Therefore, a total of 18 records were included from the SLR update (see Figure 3.2). Thirteen of these 18 records were linked to studies included in the original SLR, while five records described four unique studies not previously identified.

By completion of the update, 33 publications reporting on 15 unique studies were included. Two studies included patients with C3G who were treated with iptacopan (APPEAR-C3G and the Phase 2 trial, with open-label extension study results for patients originating from the Phase 2 trial included as linked publications for the Phase 2 trial).

Figure 3.1: PRISMA flow diagram for studies included in the original SLRAdapted from Figure 1, Appendix B, CS¹

CS = company submission; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLR = systematic literature review

Figure 3.2: PRISMA flow diagram for studies included in the SLR updateAdapted from Figure 2, Appendix B, CS⁶

ASN = American Society of Nephrology; AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CRD = Centre for Reviews and Dissemination; CS = company submission; EMA = European Medicines Agency; ERA-EDTA = European Renal Association – European Dialysis and Transplant Association; EUCTR = European Union Clinical Trials Registry; FDA = Food and Drug Administration; HAS = Haute Autorité de santé; HTA = Health Technology Assessment; ICER = Institute for Clinical and Economic Review; ICTRP = International Clinical Trials Registry Platform; INAHTA = International Network of Agencies for Health Technology Assessment; IQWiG = Institute for Quality of Efficiency in Health Care; MEDLINE = Medical Literature Analysis and Retrieval System Online; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLR = systematic literature review; SMC = Scottish Medicines Council; WCN = World Congress of Nephrology

3.2.2 Summary of details for the trials

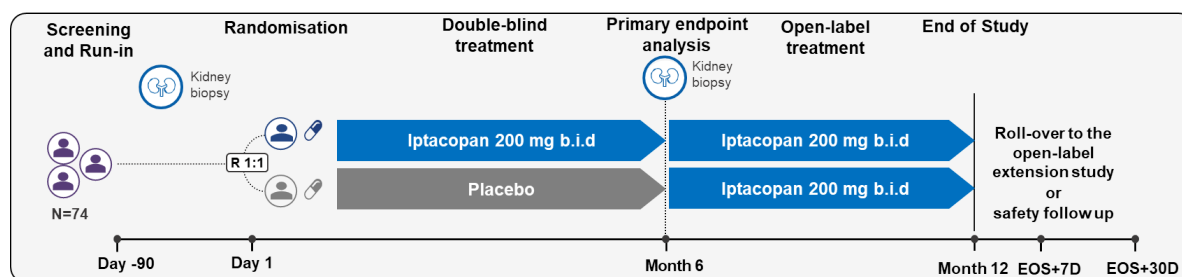
This Section will provide a summary and description of the relevant trials as they are presented and described in the CS.¹

3.2.2.1 APPEAR-C3G

APPEAR-C3G (NCT04817618) is an international, multicentre, randomised, double-blind, parallel group, placebo-controlled Phase 3 study to evaluate the efficacy and safety of iptacopan in patients with native kidney C3G.¹ It is comprised of a screening/run-in period (see Figure 3.3) lasting up to 90 days; a 6-month double-blind treatment period, during which patients received blinded treatment with 200 mg iptacopan or placebo orally b.i.d. (randomisation 1:1); and a 6-month open-label treatment period, during which all patients received open-label iptacopan 200 mg orally b.i.d.¹

Following completion of study treatment at 12 months, patients were given the option to discontinue iptacopan treatment and enter a 30-day safety follow-up period or continue iptacopan treatment by transitioning to a roll-over open-label extension.¹ This submission only considers the adult cohort of the trial, in line with the patient population described in the decision problem.¹

Figure 3.3: APPEAR-C3G study design



Adapted from Figure 6, CS¹

b.i.d. = twice daily; C3G = complement 3 glomerulopathy; CS = company submission; D = day; EOS = end of study; N = total number of patients; R = randomisation

Table 3.4: Summary of methodology: APPEAR-C3G

Parameter	Inclusion
Study design	Multicentre, randomised, double-blind, parallel group, placebo-controlled Phase 3 study
Location	Seventy-nine sites across 18 countries: UK (three sites; nine adult patients), Argentina, Brazil, Canada, China, Czechia, France, Germany, Greece, India, Israel, Italy, Japan, the Netherlands, Spain, Switzerland, Turkey, and the US
Key eligibility criteria for patients	Key inclusion criteria: - Adult patients, 18–60 years of age^a - Diagnosis of C3G as confirmed by kidney biopsy within 12 months prior to enrolment - On maximally recommended or tolerated dose of ACEi or ARB for at least 90 days prior to randomisation - MPA,^b (CoS; prednisolone ≤ 7.5 mg/day or equivalent), SGLT2is and MRAs were allowed if maintained on a stable dose for at least 90 days prior to randomisation

Parameter	Inclusion
	- UPCR ≥ 1.0 g/g (≥ 113 mg/mmol) sampled from the first morning void urine sample at Day -75 and Day -15 - eGFR (using the CKD-EPI formula⁷ or measured eGFR ≥ 30 mL/min/1.73 m² at screening and Day -15 - Reduced serum C3 (< 0.85 x lower limit of the central laboratory normal range, i.e. < 77 mg/dL) at screening - Vaccination against N. meningitidis, S. pneumoniae (mandatory) and H. influenzae (recommended) if not previously vaccinated or if a booster was required Key exclusion criteria: - Solid organ (including kidney) or cell transplant - Rapidly progressive crescentic glomerulonephritis - Kidney biopsy showing interstitial fibrosis/tubular atrophy of $> 50\%$ - Monoclonal gammopathy of undetermined significance
Trial drug(s)	Patients were randomised 1:1, stratified by CoS and/or MPA treatment at randomisation (yes versus no), to receive either: - Intervention: iptacopan (LNP023) 200 mg b.i.d. (oral capsules) for 6 months (double-blind) followed by open-label iptacopan 200 mg b.i.d. for an additional 6 months, N=38 OR: - Comparator: placebo b.i.d. (oral capsules) for 6 months (double-blind) followed by open-label iptacopan 200 mg b.i.d. for 6 months, N=36 Both iptacopan and placebo were administered on top of optimised background therapy, including ACEis/ARBs at a maximally tolerated dose, with or without CoS and/or MPA or SLGT2is, provided these therapies were maintained at a stable dose for at least 90 days prior to randomisation. The following medications were prohibited during the treatment period: cyclophosphamide, calcineurin inhibitors, eculizumab, rituximab, other standard immunosuppressant therapies (except MMF, MPS and CoS at a dose of prednisolone ≤ 7.5 mg/day or equivalent), and live vaccines.
Primary endpoint(s)^e	Double-blind (6-month) treatment period - iptacopan versus placebo: - Log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine collection) at 6 months 12-month treatment period: - CfB in log-transformed UPCR at the 12-month visit (both treatment arms) - Change in log-transformed UPCR from the 6-month visit to the 12-month visit (placebo-iptacopan switch arm only)
Secondary endpoints^e	Double-blind (6-month) treatment period - iptacopan versus placebo: - CfB in eGFR at 6 months - Proportion of patients achieving the composite renal endpoint ($\geq 50\%$ reduction in UPCR + $\leq 15\%$ reduction in eGFR compared to the baseline visit) at 6 months

Parameter	Inclusion
	- CfB in disease total activity score in a kidney biopsy at 6 months - CfB in the FACIT-Fatigue score at 6 months - Safety and tolerability 12-month treatment period: - Proportion of patients achieving the composite renal endpoint ($\geq 50\%$ reduction UPCR + $\leq 15\%$ reduction in eGFR) compared to the baseline visit at 12 months (both treatment arms) and compared to the 6-month visit at 12 months (placebo-iptacopan switch arm only) - CfB in the total activity score in a kidney biopsy at 12 months (both treatment arms) and change from the 6-month visit to the 12-month visit (placebo-iptacopan switch arm only) - CfB in the FACIT-Fatigue score at 12 months (both treatment arms) and change from the 6-month visit to the 12-month visit (placebo-iptacopan switch arm only) - Safety and tolerability
Key exploratory endpoints^d	Double-blind (6-month) treatment period - iptacopan versus placebo: - CfB in glomerular C3 deposit scores from a kidney biopsy at 6 months - CfB in circulating biomarker levels, including serum C3, AP activity, plasma B^b, plasma sC5b-9 and urinary sC5b-9/creatinine, at 6 months 12-month treatment period: - CfB in eGFR at 12 months (both treatment arms) - Change in eGFR from the 6-month visit to the 12-month visit (placebo-iptacopan switch arm only) - Change in eGFR slope - CfB in glomerular C3 deposit scores from a renal biopsy at 12 months A list of all exploratory endpoints assessed in APPEAR-C3G can be found in Appendix J of the CS.⁸
Pre-planned subgroup analyses of primary endpoint	The subgroup analysis included: - Age group - Sex - Race - Region - CoS and/or MPA at randomisation (yes versus no) - Baseline UPCR (< 3 g/g versus ≥ 3 g/g) - Baseline total urinary protein (< 3 g/day versus ≥ 3 g/day) - Baseline eGFR (< 60 mL/min/1.73 m² versus ≥ 60 mL/min/1.73 m² and < 90 mL/min/1.73 m² versus ≥ 90 mL/min/1.73 m²) - Baseline C3 (< 45 mg/dL versus ≥ 45 mg/dL) - Years since C3G diagnosis (< 2 years versus ≥ 2 years) - Age at C3G diagnosis (< 18 years versus ≥ 18 years) - C3G disease subtype at diagnosis (C3GN versus DDD) - Hypertension (yes versus no)
Adapted from Table 5, CS ¹	

Parameter	Inclusion
^a	A separate and independent cohort of adolescent patients (aged 12–17 years) with C3G was initiated later in the APPEAR-C3G study. The adolescent cohort will read out at a later date; this patient population has not been included in the initial licence application for C3G and will not be considered in this submission.
^b	MPAs such as MMF or MPS.
^c	Defined as a 50% decline in eGFR within 3 months with kidney biopsy findings of glomerular crescent formation seen in at least 50% of glomeruli.
^d	Confirmed by the measurement of serum free light chains or other investigation as per local SoC.
^e	Central laboratory testing was used for all analysis of clinical chemistry and haematology specimens, as well as urinalysis.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; b.i.d. = twice daily; C3 = complement 3; C3G = complement 3 glomerulopathy; C3GN = C3 glomerulonephritis; CfB = change from baseline; CKD = chronic kidney disease; CKD-EPI = CKD Epidemiology Collaboration; CoS = corticosteroid; CS = company submission; DDD = dense deposit disease; eGFR = estimated glomerular filtration rate; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MPS = mycophenolate sodium; MRA = mineralocorticoid receptor antagonist; RCT = randomised clinical trial; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SoC = standard of care; UK = United Kingdom; UPCR = urine protein-to-creatinine ratio; US = United States	

Seventy-four patients were enrolled in the adult cohort, with 38 patients randomised to the iptacopan arm and 36 randomised to the placebo arm. All 74 patients completed the 6-month double-blind period.¹ Two patients in the iptacopan arm discontinued double-blind treatment. Both of these patients continued double-blind study visits (without treatment) until the end of the double-blind period, and then transitioned to the open-label period where they attended study visits and received open-label Iptacopan.¹ Seventy-three patients completed the full 12 months of the study (6 months double-blind period plus 6 months open-label period). One patient originally randomised to the placebo arm discontinued treatment during the open-label period, with the reason recorded as patient decision, was lost to follow-up and discontinued from the study.¹

3.2.2.2 Supportive evidence

Two studies were identified that provide supportive evidence of the clinical efficacy of iptacopan for the treatment of patients with C3G. This is the Phase 2 study and the open label extension study. The open label extension study provide data on the long-term clinical efficacy and safety of iptacopan in C3G, as it represents the longest follow-up period in the clinical trial programme for iptacopan in C3G.¹ These trials are briefly summarised below.

3.2.2.2.1 Phase 2 Study

The Phase 2 study (NCT03832114) was an international, multicentre, open-label, single-arm, non-randomised study in adults with biopsy-confirmed C3G. Two cohorts of patients were included, one with native kidney C3G (native kidney cohort; Cohort A) and one with C3G recurrence following kidney transplantation (post-transplant recurrent cohort; Cohort B). All patients received iptacopan b.i.d. for 12 weeks. A total of 27 patients were enrolled and completed the study: 16 in the native kidney cohort and 11 in the post-transplant recurrent cohort.¹ Figure 3.4 and Table 3.3 provide details.

Table 3.5: Summary of methodology: Phase 2 study

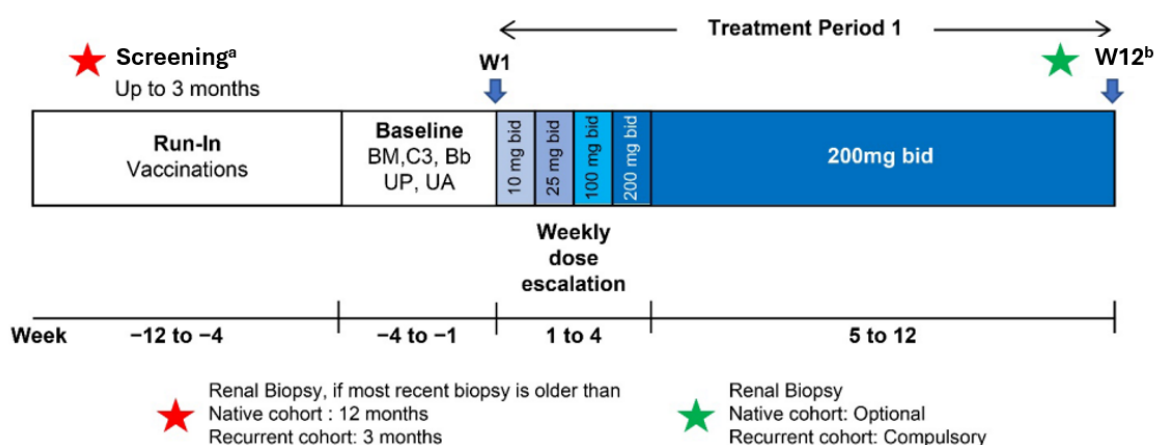
Parameter	Phase 2 study (NCT03832114)
Study design	Multicentre, open-label, two cohort, single-arm, non-randomised Phase 2 study
Location	Nine sites across six countries: • UK (two sites; eight patients), France, Germany, Italy, Spain, US

Parameter	Phase 2 study (NCT03832114)
Key eligibility criteria for patients	Native kidney cohort, N=16 (Cohort A): • Adult patients, ≥ 18 years of age • C3G confirmed by biopsy within 12 months prior to enrolment • On a maximum recommended or tolerated dose of ACEi or ARB for at least 30 days prior to treatment start • Any antiproteinuric medication at a stable dose prior to treatment start was allowed ○ MMF maintained on a stable dose for at least 30 days prior to treatment start ○ CoS maintained on a stable dose (prednisolone ≤ 7.5 mg/day or equivalent) for at least 90 days prior to treatment start • UPCR ≥ 100 mg/mmol sampled from first morning void (or ≥ 1 g/24-hour total urinary protein excretion from a 24-hour urinary collection during run-in) at run-in or at baseline • eGFR (using the CKD-EPI formula) ≥ 30 ml/min/1.73 m² • Reduced C3 at screening ($< 0.90 \times$ lower limit of the lab normal ranges) • Vaccination against N. meningitidis, S. pneumoniae and H. influenzae at least 4 weeks prior to treatment start Post-transplant recurrent cohort, N=11 (Cohort B): • Adult patients, ≥ 18 years of age • C3G recurrence after kidney transplantation confirmed by biopsy after transplantation within 12 months prior to enrolment • eGFR (using the CKD-EPI formula) ≥ 30 ml/min/1.73 m² • Normal or elevated urinary protein excretion • Vaccination against N. meningitidis, S. pneumoniae and H. influenzae at least 4 weeks prior to treatment start • On a stable dose of immunosuppression • Transplantation of a kidney allograft > 90 days before screening • No signs of allograft rejection
Trial drug	Intervention: iptacopan Treatment period 1 (12 weeks): • Dose escalation phase (Weeks 1–4) ○ Week 1: iptacopan 10 mg b.i.d. ○ Week 2: iptacopan 25 mg b.i.d. ○ Week 3: iptacopan 100 mg b.i.d. ○ Week 4: iptacopan 200 mg b.i.d. • Weeks 5–12 ○ Iptacopan 200 mg b.i.d. was administered for an additional 8 weeks, for a total duration of 9 weeks Treatment period 2: • If patients entered treatment period 2, iptacopan 200 mg b.i.d. was administered for a further 12 weeks, for a total duration of 21 weeks at the highest dose • Dose levels were tapered down in two steps before treatment ended

Parameter	Phase 2 study (NCT03832114)
Primary endpoint(s)	- Native kidney cohort: ratio to baseline in UPCR derived from 24-hour urine collection at Week 12 - Post-transplant recurrent cohort: CfB to Week 12 in C3 deposit score based on immunofluorescence microscopy of kidney biopsy tissue
Secondary endpoints	- Biomarker levels of blood Bb 24-hour urine UPCR and UACR - Change in and evolution of urinary albumin, urinary protein excretion, UACR, UPCR, serum creatinine, eGFR, creatinine clearance, haematuria - C3 level - Safety and tolerability - Plasma and urine PK assessments - Ratio to baseline of UPCR and UACR (post-transplant recurrent cohort only)
Adapted from Table 22, CS ¹ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; b.i.d. = twice daily; Bb = cleaved Factor b; C3 = complement 3; C3G = complement 3 glomerulopathy; CfB = change from baseline; CKD = chronic kidney disease; CKD-EPI = CKD Epidemiology Collaboration; CoS = corticosteroid; eGFR = estimated glomerular filtration rate; MMF = mycophenolate mofetil; MPA = mycophenolic acid; PK = pharmacokinetics; RCT = randomised clinical trial; UACR = urine albumin-to-creatinine ratio; UK = United Kingdom; UPCR = urine protein-to-creatinine ratio; US = United States	

The trial included a screening period comprised of run-in (≤ 60 days) and a 30-day baseline period. Patients then entered treatment period 1 (12 weeks), with dose escalation of iptacopan up to 200 mg b.i.d. At Week 12, kidney biopsies were collected; which were optional for the native kidney cohort but mandatory for the post-transplant recurrent cohort.¹ Following 12 weeks of treatment in the Phase 2 study, patients could roll over to the extension study if treatment continuation was found to be beneficial. If continuation of treatment was not deemed beneficial by the investigator, study medication was titrated down to 25 mg once daily for 7 days, followed by 10 mg once daily for a further 7 days. The patient then continued in the follow-up period (12 weeks) until the end-of-study (EOS) visit.¹

Figure 3.4: Phase 2 study design



Adapted from Figure 17, CS¹

^a Run-in period could be extended to ensure stable doses of ACEi/ARB, MMF, and or CoS.

^b Patients may roll over into a separate extension study at Week 12.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker, Bb = cleaved factor b; b.i.d. = twice daily; BM = biomarkers; C3 = component C3; CoS = corticosteroid; CS = company submission; MMF = mycophenolate mofetil; UA = urinary albumin; UP = urinary protein; W = week

Twenty-seven patients (16 patients in the native kidney cohort and 11 patients in the post-transplant recurrent cohort) were enrolled and treated with iptacopan. All patients completed the 12-week study and there were no discontinuations. Twenty-six of these patients (96.3%) then rolled over into the open-label extension study (NCT03955445) to continue long-term treatment. One patient in the post-transplant recurrent cohort did not roll over and completed the tapering down and the follow-up period.¹

3.2.2.2.2 Open label extension study

The open-label extension study (NCT03955445) is an ongoing, non-randomised study in patients receiving open-label iptacopan after completing treatment in APPEAR-C3G or the Phase 2 study detailed above.

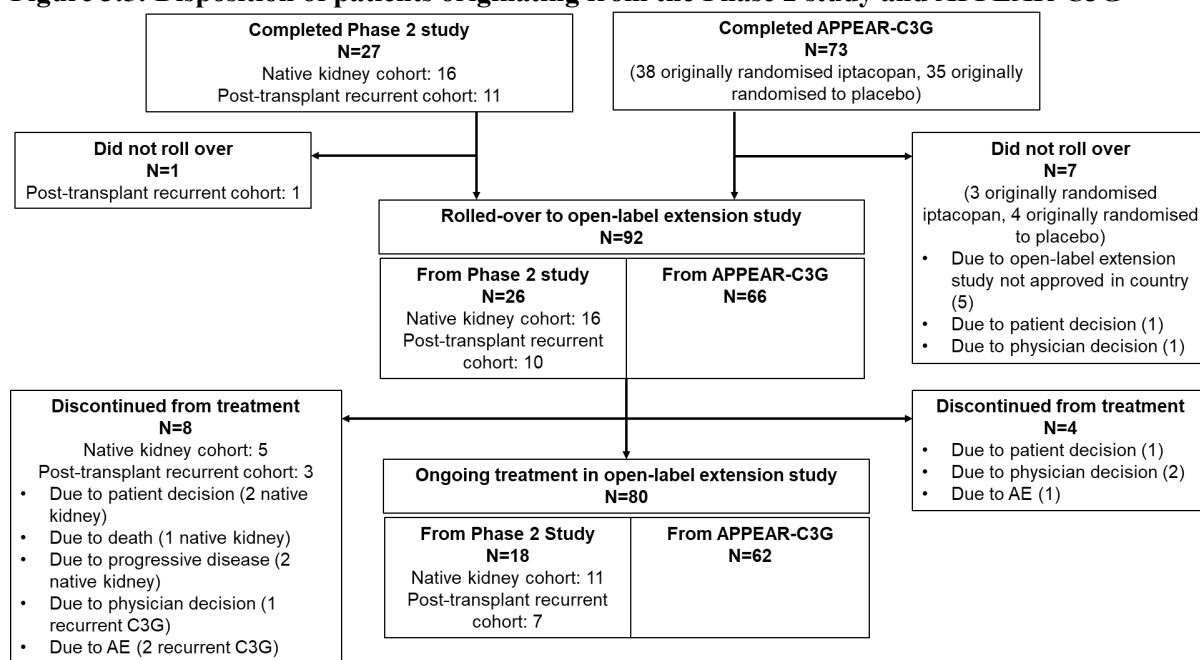
Table 3.6: Summary of methodology: Open-label extension study

Parameter	Open-label extension study (NCT03955445)
Study design	Open-label, non-randomised extension study
Location	Thirty-three sites across 17 countries: UK (three sites; nine patients originating from APPEAR-C3G and eight patients originating from the Phase 2 study), Argentina, Brazil, Canada, China, Czechia, France, Germany, Greece, Israel, Italy, Japan, the Netherlands, Spain, Switzerland, Turkey, US
Eligibility criteria for patients	Patients must have completed the treatment period of APPEAR-C3G or the Phase 2 study on study drug.
Trial drug	Iptacopan 200 mg b.i.d.
Primary endpoints	- Patients originating from the native kidney cohort of the Phase 2 study: number of patients who achieve the composite renal endpoint at the 9-month visit (stable or improved eGFR [$\leq 10\%$ reduction] compared to the baseline visit in the Phase 2 study and either $\geq 50\%$ reduction in UPCR compared to baseline or reduction in UPCR to < 300 mg/g and either a $\geq 50\%$ increase in C3 compared to baseline or an increase in C3 to ≥ 90 mg/dL [i.e. $\geq$ the lower limit of normal]) - Patients originating from the post-transplant recurrent cohort of the Phase 2 study: CfB in the C3 deposit score at the 6- to 9-month visit compared to the baseline visit in the Phase 2 study - All patients: long-term safety and tolerability of iptacopan
Secondary endpoints	Secondary endpoints are presented in Appendix J.2.2
Adapted from Table 24, CS ¹ b.i.d. = twice daily; C3 = complement component 3; C3G = complement 3 glomerulopathy; CfB = change from baseline; CS = company submission; eGFR = estimated glomerular filtration rate; UPCR = urine protein-to-creatinine ratio; UK = United Kingdom; US = United States	

Ninety-two adults entered the open-label extension study (see Figure 3.5): 26 patients out of the 27 patients who had completed the Phase 2 study and 66 patients out of the 73 patients who had completed APPEAR-C3G. As of the data cut-off date of 6 May 2024, 80 patients (18 from the Phase 2 study and 62 from APPEAR-C3G) were ongoing on treatment in the study. The overall 12 treatment discontinuations were due to patient decision (n=3), physician decision (n=3), adverse event (AE) (n=3), progressive disease (n=2), and death (n=1).¹ Among the 26 patients who entered the extension study from the Phase 2 study, 22 patients had ≥ 2 years of treatment, 20 patients had ≥ 3 years of treatment, and 13 patients had ≥ 4 years of iptacopan treatment. The mean duration of treatment was 3.6 years (standard deviation [SD]: 1.2 years). Among the 66 patients who entered the extension study

from APPEAR-C3G, 53 (71.6%) completed the 15-month visit, 36 (48.6%) completed the 18-month visit, 27 (36.5%) completed the 21-month visit and 13 (17.6%) completed the 24-month visit at the time of data cut-off.¹

Figure 3.5: Disposition of patients originating from the Phase 2 study and APPEAR-C3G



Adapted from Figure 20, CS¹

AE = adverse event; C3G = complement 3 glomerulopathy; CS = company submission; N = total number of patients

3.2.3 Statistical analysis of included trials

The CS¹ provides a tabulated oversight of the statistical methods utilised in the APPEAR-C3G trial which is detailed below.

Table 3.7: Statistical overview of APPEAR-C3G

APPEAR-C3G	Description
Analysis sets	• SCR: included all patients screened during the study. • RAS: included all randomised patients. • FAS: included all patients to whom study treatment was assigned by randomisation. According to the intent-to-treat principle, patients were analysed according to the treatment they were assigned to, considering the actual CoS and/or MPA use at randomisation (stratification factor) ○ The FAS was used for the primary analysis of the double-blind period, and for efficacy analyses where the entire data from the double-blind period and the open-label period of all patients were used. The FAS excluded any patients without a randomisation number and those who were mis-randomised • CFAS: included all patients randomised to the iptacopan arm and all patients randomised to the placebo arm who were then treated with iptacopan in the open-label period. ○ This analysis set was used to analyse iptacopan efficacy data and the analysis considered all data collected after the first administration of

APPEAR-C3G	Description
	iptacopan. This excluded any patients without a randomisation number, those who were mis-randomised and patients who were randomised to placebo but not treated with iptacopan in the open-label period • SAF: included all patients who received at least one dose of study treatment. Patients were analysed according to the study treatment they received • CSAF: included all patients who received at least one dose of iptacopan during the double-blind treatment period or the open-label treatment period ○ The CSAF was used to analyse long-term iptacopan safety data, and the analysis considered all data collected after the first administration of iptacopan
Statistical analysis of primary endpoint(s)	Primary analysis of the 6-month double-blind period: <i>Hypothesis:</i> • That iptacopan is superior to placebo in reducing proteinuria at 6 months of treatment. • The null hypothesis that the mean of the log-transformed ratio to baseline of UPCR at month 6 for the iptacopan group is greater than or equal to that of the placebo group ($H_0: \mu_{\text{iptacopan}} - \mu_{\text{placebo}} \geq 0$) was tested against a one-sided alternative hypothesis of the mean for the iptacopan group being less than that for the placebo group ($H_A: \mu_{\text{iptacopan}} - \mu_{\text{placebo}} < 0$) • <i>Statistical testing</i> • The primary comparison between iptacopan and placebo was defined as a one-sided hypothesis, which was tested at the one-sided 0.025 level • The primary analyses were based on the FAS • At baseline and month 6, the geometric mean of two 24-hour UPCR values obtained from two distinct 24-hour urine collections was used in the analysis as the 24-hour UPCR measurement for that visit. In case only one 24-hour UPCR value was available, that value was used as the 24-hour UPCR measurement for that visit in the analysis • 24-hour UPCR measurements collected after initiation or intensification of antiproteinuric therapies or KRT were imputed, to reflect a poor response and also to reflect that 24-hour UPCR levels would deteriorate (increase) had these treatments not been received • Statistical analysis was performed using a MMRM for the log ratio to baseline in UPCR measurements. This model included treatment, time point, CoS and/or MPA at randomisation (yes versus no) as fixed effects, treatment*time point as interaction term and log (baseline UPCR) as covariate. The correlations between visits within patients were modelled using an unstructured covariance matrix. The Kenward-Roger adjustment for degrees of freedom was used • If there were intercurrent events occurring in the study, the analysis was carried out in the imputed datasets. Each imputed dataset was analysed using the MMRM and the results were combined using Rubin's rules • The ratio of geometric means (iptacopan versus placebo) was presented for the 6-month time point together with the two-sided 95% CI and one-sided p-value for the hypothesis test. The study was considered positive if the one-sided p-value for the hypothesis test was <0.025

APPEAR-C3G	Description
	<i>Handling of intercurrent events</i> - Initiation or intensification of antiproteinuric therapies after randomisation: values after the intake of additional antiproteinuric therapies were set to missing and imputed using the “jump to reference” approach⁹ the iptacopan arm and the MAR assumption for the placebo arm (hypothetical strategy) - Initiation of KRT after randomisation: Values after initiation of KRT were imputed using the J2R approach⁹ for the iptacopan arm and the MAR assumption for the placebo arm (hypothetical strategy) - Treatment discontinuation for any reason (other than the antiproteinuric therapies or KRT): 24-hour UPCR measurements after discontinuation of study treatment were collected and used in the analysis (treatment policy strategy) <i>Handling of missing values not related to intercurrent events</i> - The MMRM model used for the primary analysis implicitly imputes missing data under a MAR assumption
Statistical analysis of secondary endpoint(s)	Secondary endpoint analyses of the 6-month double-blind period: Analyses were performed based on the FAS. Full details on the statistical approaches to measuring CfB in UPCR, CfB in eGFR, CfB in glomerular C3 deposit scores, circulating biomarker levels, histology total activity score and FACIT-Fatigue total score, and the proportion of patients who achieved the composite renal endpoint are presented in Appendix J.1.3 <i>Multiple test procedure</i> The hypotheses associated with the secondary endpoints were to be tested only if the null hypothesis associated with the primary endpoint was rejected. A multiple test procedure was used for testing the hypotheses associated with four secondary endpoints. Given the ultra-rare nature of the disease, the multiple test procedures controlled the familywise error rate of the secondary endpoints at one-sided 0.05 <i>Handling of intercurrent events for secondary analyses</i> In general, the same strategy as described for the primary endpoint was employed for handling intercurrent events applicable to the secondary endpoints. For the composite renal endpoint, the initiation or intensification of antiproteinuric therapies or initiation of KRT were considered as treatment failures via the composite strategy <i>Handling of missing values not related to intercurrent events for secondary analyses</i> In general, missing data were handled in the same way as described for the primary analysis. For the composite renal endpoint, patients were considered as treatment failures (i.e. non-responder imputation) in case of study discontinuation due to AE or renal death
Sample size, power calculation	The sample size was calculated to sufficiently power for testing the superiority of iptacopan versus placebo on proteinuria reduction (the primary endpoint of log-transformed ratio to baseline in UPCR at 6 months)

APPEAR-C3G	Description
	- Assuming a reduction in UPCR of 60% in the iptacopan group versus 20% in the placebo group (i.e. a relative reduction versus placebo in UPCR of 50%) and a SD of 0.69 (on the log-scale) based on an interim analysis of the Phase 2 study, a sample size of 34 patients per group (total 68 patients) provided at least 98% power at a 1-sided significance level of 0.025 - Assuming a reduction in UPCR of 50% in the iptacopan group versus 20% in the placebo group (i.e. a relative reduction versus placebo in UPCR of 37.5%), a sample size of 68 patients provided at least 80% power at the 1-sided 0.025 significance level
Adapted from Table 9, CS ¹ C3G = complement 3 glomerulopathy; CFAS = combined full analysis set; Cfb = change from baseline; CI = confidence interval; CoS = corticosteroid; CS = company submission; CSAF = combined safety analysis set; eGFR = estimated glomerular filtration rate; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FAS = full analysis set; J2R = jump to reference; KRT = kidney replacement therapy; MAR = missing-at-random; MMRM = mixed model for repeated measures; MPA = mycophenolic acid; RAS = randomised analysis set; SAF = safety set; SCR = screening set; SD = standard deviation; UPCR = urine protein-to-creatinine ratio	

EAG comment: The EAG considers that the statistical analysis approach used by the company appears to be satisfactory.

3.2.4 Baseline characteristics

Baseline characteristics were provided in the CS¹ to describe the relevant populations. In the APPEAR-C3G trial 74 patients enrolled in the study, 47 were male (63.5%) and 27 were female (36.5%). The majority of patients were of White race (68.9%) and from study sites in Europe (55.4%). The mean (SD) age of all patients was 27.9 (10.7) years.

The CS states that ‘*The treatment arms were generally balanced; however, there were imbalances between groups in some baseline disease characteristics*’.¹ The EAG considers any differences between groups of 5% to be relevant and noteworthy. We do not necessarily make the claim that such differences will reflect clinical or statistically meaningful difference, but we emphasise this to ensure that this is taken into consideration when interpreting the results. The iptacopan group had more males than the placebo group (71.1% versus 55.6%), as well as differences in baseline urine protein-to-creatinine ratio (UPCR) (24-hours) ≥ 339 g/mol [3 g/g] (55.3% versus 30.6%). The iptacopan arm had notably lower eGFR at baseline, compared with those from the placebo arm (89.30 versus 99.22) with more patients having an eGFR at baseline of <60 ml/min/1.73 m² (26.3% versus 11.1%), and less at ≥ 60 ml/min/1.73 m² (73.7% versus 88.9%) (see Table 3.8). The EAG considers such imbalances to be significant and impactful.

Table 3.8: APPEAR-C3G baseline demographics and disease characteristics (FAS)

	Iptacopan (N=38)	Placebo (N=36)	Total (N=74)
Baseline demographics			
Age (years), Mean (SD)	26.1 (10.39)	29.8 (10.79)	27.9 (10.68)
Gender, n (%)			
Male	27 (71.1)	20 (55.6)	47 (63.5)
Female	11 (28.9)	16 (44.4)	27 (36.5)
Race, n (%)			

	Iptacopan (N=38)	Placebo (N=36)	Total (N=74)
White	27 (71.1)	24 (66.7)	51 (68.9)
Black or African American	1 (2.6)	1 (2.8)	2 (2.7)
Asian	9 (23.7)	9 (25.0)	18 (24.3)
American Indian or Alaska Native	0	1 (2.8)	1 (1.4)
Multiple	0	1 (2.8)	1 (1.4)
Unknown	1 (2.6)	0	1 (1.4)
Region, n (%)			
North America	7 (18.4)	8 (22.2)	15 (20.3)
Europe	22 (57.9)	19 (52.8)	41 (55.4)
Other	9 (23.7)	9 (25.0)	18 (24.3)
Baseline disease characteristics			
Baseline UPCR 24-hour (g/mol)	434.92 (258.529)	331.09 (193.208)	384.41 (233.462)
Arithmetic mean (SD)	376.20 (315.631–448.399)	291.30 (246.127–344.765)	332.19 (293.856–375.519)
Geometric mean (95% CI)			
Baseline UPCR 24-hour [g/g]			
Arithmetic mean (SD)	3.85 (2.288)	2.93 (1.710)	3.40 (2.066)
Geometric mean (95% CI)	3.33 (2.793–3.968)	2.58 (2.178–3.051)	2.94 (2.600–3.323)
Baseline UPCR (24-hour), n (%)			
<339 g/mol [3 g/g]	17 (44.7)	25 (69.4)	42 (56.8)
≥339 g/mol [3 g/g]	21 (55.3)	11 (30.6)	32 (43.2)
Baseline eGFR [ml/min/1.73 m²]			
Mean (SD)	89.30 (35.198)	99.22 (26.880)	94.12 (31.612)
Baseline eGFR, n (%)			
<90 ml/min/1.73m²	19 (50.0)	12 (33.3)	31 (41.9)
≥90 ml/min/1.73m²	19 (50.0)	24 (66.7)	43 (58.1)
Baseline eGFR, n (%)			
<60 ml/min/1.73m²	10 (26.3)	4 (11.1)	14 (18.9)
≥60 ml/min/1.73m²	28 (73.7)	32 (88.9)	60 (81.1)
Baseline C3 [mg/L]			
Arithmetic mean (SD)	316.8 (243.41)	339.3 (227.96)	327.8 (234.68)
Geometric mean (95% CI)	219.5 (160.09–300.99)	250.0 (184.39–338.88)	233.8 (188.64–289.86)
Baseline C3, n (%)			
<450 mg/L	28 (73.7)	26 (72.2)	54 (73.0)
≥450 mg/L	10 (26.3)	10 (27.8)	20 (27.0)
Hypertension^a, n (%)			
Yes	23 (60.5)	18 (50.0)	41 (55.4)
No	15 (39.5)	18 (50.0)	33 (44.6)
Age at C3G diagnosis, years			

	Iptacopan (N=38)	Placebo (N=36)	Total (N=74)
Mean (SD)	22.0 (10.88)	25.3 (10.80)	23.6 (10.90)
Age at C3G diagnosis, n (%)			
<18 years	15 (39.5)	6 (16.7)	21 (28.4)
≥18 years	23 (60.5)	30 (83.3)	53 (71.6)
Time since first C3G diagnosis, years			
Mean (SD)	4.60 (4.443)	4.82 (6.046)	4.71 (5.248)
Time since first C3G diagnosis, n (%)			
<2 years	15 (39.5)	15 (41.7)	30 (40.5)
≥2 years	23 (60.5)	21 (58.3)	44 (59.5)
C3G subtype at diagnosis, n (%)			
C3GN	26 (68.4)	32 (88.9)	58 (78.4)
DDD	9 (23.7)	1 (2.8)	10 (13.5)
Mixed C3GN/DDD	2 (5.3)	2 (5.6)	4 (5.4)
Unknown	1 (2.6)	1 (2.8)	2 (2.7)
Source: Adapted from Table 7, CS.¹ Baseline 24-hour UPCR refers to UPCR as measured by the geometric mean of two 24-hour urine collections at baseline/Day 1. Baseline total urinary protein 24-hour refers to total urinary protein as measured by the geometric mean of two 24-hour urine collections at baseline/Day 1. Baseline eGFR was defined as the arithmetic mean of two eGFR values at Day -15 visit and Day 1 visit. ^a Hypertension is defined based on “hypertension at diagnosis” from C3G medical history and the reported hypertension terms from the medical history. C3 = complement 3; C3G = complement 3 glomerulopathy; C3GN = C3 glomerulonephritis; CI = confidence interval; CS = company submission; DDD = dense deposit disease; eGFR = estimated glomerular filtration rate; FAS = full analysis set; RAS = renin angiotensin system; SD = standard deviation; UPCR = urine protein-to-creatinine ratio			

The EAG asked the company to provide information on how these differences between the characteristics of the two arms would impact the results.³ In their response to the request for clarification, the company stated that ‘...*The baseline imbalances suggest a more severe disease phenotype in the participants in the iptacopan arm. This was also noted by UK clinicians participating in an advisory board, and they suggested that due to this, comparisons between iptacopan and placebo groups may therefore underestimate the iptacopan treatment effect*’.⁴

As a consequence of these acknowledged imbalances, the company provided details on post hoc analyses which were described within the CS but also replicated in the clarification response.⁴ The company stated that ‘*The results of these post-hoc sensitivity analyses were consistent with the results of the primary analysis, suggesting that these baseline imbalances did not impact the UPCR endpoint*’.⁴

The company also stated that ‘*The pre-specified analysis of C₃B in eGFR included the background immunosuppression stratification factor (corticosteroids and/or mycophenolic acid treatment at randomisation) and baseline eGFR as covariates. Additional post-hoc sensitivity analyses were carried out to assess the impact of adjusting for other baseline covariates where imbalances had been observed. ...The adjustments for age at C3G diagnosis or subtype of C3G yielded results consistent with the pre-specified analysis.*’ The company emphasize that ‘*the C₃B in eGFR analysis adjusted for baseline UPCR resulted in a larger numerical improvement for iptacopan versus placebo when compared to the pre-*

specified analysis, with an adjusted mean difference of 3.20 mL/min/1.73 m² for iptacopan versus placebo (95% CI: -1.61, 8.01) compared to the pre-specified analysis with a mean difference of 2.16 mL/min/1.73 m² (95% CI: -2.75, 7.06)⁴.

The company provide tabulated data relevant to this. Table 3.9 presents post-hoc sensitivity analyses for primary endpoint change from baseline (CfB) in UPCR at Month 6. Table 3.10 presents post-hoc sensitivity analyses for secondary endpoint CfB in eGFR (mL/min/1.73 m²) at Month 6.

Table 3.9: Post-hoc sensitivity analyses for primary endpoint CfB in UPCR at Month 6 (FAS)

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		% Reduction (95% CI)	1-sided p-value
Log-transformed ratio to baseline in UPCR (sampled from 24-hour urine collection) at Month 6	Primary analysis		
	Primary analysis	35.1 (13.8, 51.1)	0.0014
	Post-hoc sensitivity analyses		
	Post-hoc sensitivity analysis 1: Adjustment for baseline eGFR (mL/min/1.73 m ²)	35.0 (13.4, 51.2)	0.0016
	Post-hoc sensitivity analysis 2: Adjustment for age group at C3G diagnosis ^a	35.8 (14.2, 52.0)	0.0014
	Post-hoc sensitivity analysis 3: Adjustment for C3G subtype at diagnosis ^b	38.4 (17.5, 54.1)	0.0006
Based on Table 6 of response to clarification ⁴ ^a Age group at C3G diagnosis was categorised as <18 years and ≥18 years. ^b C3G subtype at diagnosis was categorised as C3GN and other. b.i.d. = twice daily; C3G = C3 glomerulopathy; C3GN = C3 glomerulonephritis; CfB = change from baseline; CI = confidence interval; eGFR = estimated glomerular filtration rate; FAS = full analysis set; UPCR = urine protein-to-creatinine ratio			

Table 3.10: Post-hoc sensitivity analyses for secondary endpoint CfB in eGFR (mL/min/1.73 m²) at Month 6 (FAS)

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		Adj. mean difference (95% CI)	1-sided p-value
Change from baseline in eGFR (mL/min/1.73 m ²) at Month 6	Pre-specified analysis		
	Pre-specified analysis	2.156 (-2.749, 7.061)	0.1945
	Post-hoc sensitivity analyses		
	Post-hoc sensitivity analysis 1: Adjustment for baseline UPCR 24-hour (g/g)	3.199 (-1.614, 8.012)	0.0963
	Post-hoc sensitivity analysis 2: Adjustment for age group at C3G diagnosis ^a	2.374 (-2.622, 7.369)	0.1759
	Post-hoc sensitivity analysis 3:	2.068 (-2.952, 7.088)	0.2097

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		Adj. mean difference (95% CI)	1-sided p-value
	Adjustment for C3G subtype at diagnosis ^b		
Adapted from Table 7, response to clarification ⁴ ^a Age group at C3G diagnosis was categorised as <18 years and ≥18 years. ^b C3G subtype at diagnosis was categorised as C3GN and other. b.i.d. = twice daily; C3G = C3 glomerulopathy; C3GN = C3 glomerulonephritis; Cfb = change from baseline; CI = confidence interval; eGFR = estimated glomerular filtration rate; FAS = full analysis set; UPCR = urine protein-to-creatinine ratio			

Furthermore, the EAG had additional concerns regarding the baseline characteristics and asked the company to provide the baseline data of all UK based participants. In the response to clarification⁴ the company provided the following Table 3.11.

Table 3.11: APPEAR-C3G baseline characteristics for UK participants

	Iptacopan (N=■)	Placebo (N=■)	Total (N=9)
Baseline demographics			
Age (years)			
Mean (SD)	■	■	■
Gender, n (%)			
Male	■	■	■
Female	■	■	■
Race, n (%)			
White	■	■	■
Region, n (%)			
Europe	■	■	■
Baseline disease characteristics			
Baseline UPCR 24-hour (g/mol)			
Arithmetic mean (SD)	■	■	■
Geometric mean (95% CI)	■	■	■
Baseline UPCR 24-hour [g/g]			
Arithmetic mean (SD)	■	■	■
Geometric mean (95% CI)	■	■	■
Baseline UPCR (24-hour), n (%)			
<339 g/mol [3 g/g]	■	■	■
≥339 g/mol [3 g/g]	■	■	■
Baseline eGFR [ml/min/1.73 m²]			
Mean (SD)	■	■	■
Baseline eGFR, n (%)			
<90 ml/min/1.73m ²	■	■	■

	Iptacopan (N=■)	Placebo (N=■)	Total (N=9)
≥ 90 ml/min/1.73m ²	■	■	■
Baseline eGFR, n (%)			
<60 ml/min/1.73m ²	■	■	■
≥ 60 ml/min/1.73m ²	■	■	■
Baseline C3 [mg/L]			
Arithmetic mean (SD)	■	■	■
Geometric mean (95% CI)	■	■	■
Baseline C3, n (%)			
<450 mg/L	■	■	■
≥ 450 mg/L	■	■	■
Hypertension^a, n (%)			
Yes	■	■	■
No	■	■	■
Age at C3G diagnosis, years			
Mean (SD)	■	■	■
Age at C3G diagnosis, n (%)			
<18 years	■	■	■
≥ 18 years	■	■	■
Time since first C3G diagnosis, years			
Mean (SD)	■	■	■
Time since first C3G diagnosis, n (%)			
<2 years	■	■	■
≥ 2 years	■	■	■
C3G subtype at diagnosis, n (%)			
C3GN	■	■	■
Unknown	■	■	■

Adapted from Table 8, response to clarification.⁴

Baseline 24-hour UPCR refers to UPCR as measured by the geometric mean of two 24-hour urine collections at baseline/Day 1.

Baseline total urinary protein 24-hour refers to total urinary protein as measured by the geometric mean of two 24-hour urine collections at baseline/Day 1.

Baseline eGFR was defined as the arithmetic mean of two eGFR values at Day – 15 visit and Day 1 visit.

^a Hypertension is defined based on “hypertension at diagnosis” from C3G medical history and the reported hypertension terms from the medical history.

C3 = complement 3; C3G = complement 3 glomerulopathy; C3GN = C3 glomerulonephritis; CI = confidence interval; eGFR = estimated glomerular filtration rate; FAS = full analysis set; RAS = renin angiotensin system; SD = standard deviation; UK = United Kingdom; UPCR = urine protein-to-creatinine ratio

It is clear from the table above that there were minimal UK based participants involved in this trial with only nine in total. Minor imbalances beyond 5% were present across some characteristics including but not limited to those in the iptacopan group being younger and having more patients with lower

eGFR (<60 ml/min/1.73 m²). However, given the small sample of nine, differences by proportion will obviously be larger and appear more pronounced, when in reality these differences reflect only a few patients. The EAG therefore, does not consider these to be remarkable, however the presentation of data that has so few UK based participants does not allow for consideration of meaningful generalisability.

A particular interest to the EAG was how the data in this submission could be generalised to the population of England and Wales. The EAG requested information on this and in the company's response stated that *'in a UK advisory board, clinical experts were aligned that the inclusion criteria of the APPEAR-C3G and Phase 2 trials were valid, and that the trial populations were reflective of patients with C3G seen in UK clinical practice. For example, the advisors agreed that the concomitant medications (including ACEi/ARBs) in APPEAR-C3G were appropriate and representative of management of C3G patients within UK clinical practice, and that C3G patients generally present with UPCR levels well above 1 g/g (≥113 mg/mmol). The trial generalisability to the C3G population in England and Wales was further supported by the fact that several UK study sites had participated in the trials'*⁴.

The company go on to provide tabulated data showing a comparison of patient characteristics in APPEAR-C3G and the C3G population of National Registry of Rare Kidney Diseases (RaDaR) data from patients with C3G in the UK which reflects the clinical characteristics of relevant UK based patients. The EAG noted that the RaDaR study indicated that the baseline patient characteristics in the APPEAR-C3G potentially do not accurately reflect UK clinical practice as the proportion of females in APPEAR-C3G is lower and the clinical characteristics (e.g. mean eGFR and chronic kidney disease [CKD] stage) do seem to reflect a healthier population in APPEAR-C3G. However, the company reiterated that *'Median age at diagnosis was similar in APPEAR-C3G and the RaDaR cohort. Age at latest follow-up was higher in the prevalent RaDaR cohort than in APPEAR-C3G patients at baseline. The lower percentage of females in APPEAR-C3G (36.5%) compared to RaDaR (47%) was noted by UK clinicians as a common finding in clinical trials, especially in young age groups where pregnancy is a concern.'*⁴

Table 3.12: APPEAR-C3G and RaDaR disease characteristics

	APPEAR-C3G (N=74)	RaDaR at diagnosis (N=258)	RaDaR at latest follow-up ^c (N=240)
Age at C3G diagnosis (years)			
Mean (SD)	23.6 (10.9)	28.9 (20.24)	NR
Median	20.0	21.8	
Current age (years)^a			
Mean (SD)	27.9 (10.68)	N/A	40.6 (19.34)
Median	23.0		36.4
Gender, n (%)			
Male	47 (63.5)	139 (54)	128 (53)
Female	27 (36.5)	119 (46)	112 (47)
Race, n (%)			
White	51 (68.9)	203 (79)	186 (78)
Black or African American	2 (2.7)	NR	NR
Asian	18 (24.3)	NR	NR
American Indian or Alaska Native			

	APPEAR-C3G (N=74)	RaDaR at diagnosis (N=258)	RaDaR at latest follow-up ^c (N=240)
Multiple	1 (1.4)	NR	NR
Other	1 (1.4)	NR	NR
Unknown	NR	25 (10)	24 (10)
	1 (1.4)	30 (12)	30 (13)
UPCR at diagnosis (g/g)		(N=91)	
Arithmetic mean (SD)	3.98 (3.14)	6.04 (11.87) ^b	NR
Current UPCR (g/g)^a			(N=38)
Arithmetic mean (SD)	3.40 (2.07)	N/A	1.73 (2.64) ^b
eGFR at diagnosis (ml/min/1.73 m²)		(N=109)	
Mean (SD)	110.60 (33.96)	70 (38.1)	NR
Current eGFR (ml/min/1.73 m²)^a			(N=62)
Mean (SD)	94.12 (31.61)	N/A	67 (40.3)
Adapted from Table 9, response to clarification. ⁴ ^a “Current” in relation to APPEAR-C3G refers to values at baseline. ^b Reported in mg/mmol in RaDaR data, converted to g/g by dividing by 113. Original reported values: RaDaR at latest follow-up, mean (SD) 196 (297.9) mg/mmol; RaDaR at diagnosis, mean (SD) 682 (1340.8) mg/mmol. ^c Prevalent population. At latest follow-up reflects measurement within the last year. Patients who are on KRT are excluded from the prevalent population laboratory results. C3G = complement 3 glomerulopathy; eGFR = estimated glomerular filtration rate; KRT = kidney replacement therapy; N/A = not applicable; NR = not reported; RaDaR = National Registry of Rare Kidney Diseases; SD = standard deviation; UPCR = urine protein-to-creatinine ratio			

The company in their response made several supporting remarks including:⁴

‘RaDaR patients were, on average, diagnosed with higher UPCR and a lower eGFR, indicating more advanced disease at time of diagnosis, than patients enrolled in APPEAR-C3G. Baseline mean UPCR of APPEAR-C3G participants was higher (3.40 g/g) compared to the prevalent RaDaR cohort (1.73 g/g)’

‘UK clinicians confirmed that the APPEAR-C3G UPCR inclusion criterion was reflective of a population who they would intend to use iptacopan in’

‘Higher mean eGFR at baseline in APPEAR-C3G patients (94.12 mL/min/1.73m²) than in the prevalent RaDaR cohort (67 mL/min/1.73m²) may partially be related to the higher eGFR at diagnosis compared to UK clinical practice but is also influenced by the APPEAR-C3G eGFR inclusion criterion of ≥ 30 mL/min/1.73m² at screening.’

‘UK clinicians advised that they would generally want to start iptacopan treatment as soon as possible after C3G diagnosis’,

‘Overall, UK clinicians confirmed that the patients included in APPEAR-C3G and the Phase 2 study (patients with post-transplant recurrence) reflected patients who they considered would benefit from iptacopan in UK clinical practice and considered the trial data generalisable.’

The company included in their submission a copy of the clinical advisory board report which they cited as support of their defences. It is stated by the advisory board that *‘There was consensus among the experts that the inclusion/exclusion criteria of the APPEAR-C3G and Phase 2 trials were valid and that the trial populations were reflective of patients with C3G seen in UK clinical practice. They also highlighted that several UK study sites had participated in the trials and the inclusion of UK patients further supported the generalisability of trial data’*.¹⁰⁻¹²

The baseline characteristics of the Phase 2 trial are included below. Patients enrolled in the post-transplant recurrent cohort were on average older than patients in the native kidney cohort, with lower mean UPCr and eGFR at baseline.

Table 3.13: Phase 2 study baseline demographics and disease characteristics

	Native kidney cohort (N=16)	Post-transplant recurrent cohort (N=11)
Baseline demographics		
Age (years), Mean (SD)	26.1 (10.57)	34.5 (18.32)
Gender, n (%)		
Male	10 (63)	8 (73)
Female	6 (38)	3 (27)
Race, n (%)		
Caucasian	16 (100)	9 (82)
Black or African American	-	1 (9)
American Indian or Alaska Native	-	1 (9)
Baseline disease characteristics		
UPCR, Mean (SD)		
24-hour UPCR (g/mol)	454.0 (242.16)	112.3 (178.05)
eGFR (ml/min/1.73 m ²), Mean (SD)	70.1 (35.10)	52.2 (17.29)
C3 deposit score, a Median (range) (n)	-	3.0 (0.0–12.0) [n=10]
Concomitant therapy, n (%)		
ACEi	12 (75.0)	4 (36.4)
ARB	4 (25.0)	2 (18.2)
MPA (MMF or MPS)	5 (31.3)	9 (81.8)
CoS	3 (18.8)	9 (82.0)
Calcineurin inhibitors	0	11 (100.0)
Adapted from Table 23, CS ¹ Data are presented as mean (SD) unless stated otherwise. For all 24-hour urine collection parameters, baseline was defined to be the collection on Day –1 to Day 1. For eGFR, baseline was defined to be the last available assessment prior to the first dose of study drug. ^a Baseline kidney biopsy was collected during the run-in period if the most recent biopsy was older than 3 months. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; C3 = complement component 3; CoS = corticosteroid; CS = company submission; eGFR = estimated glomerular filtration rate; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MPS = mycophenolate sodium; N = total number of patients; n = number of patients; SD = standard deviation; UPCR = urinary protein-to-creatinine ratio		

EAG comment: The EAG noted that there were imbalances in relevant baseline characteristics between the intervention arm and control arm of the APPEAR-C3G trial. The EAG asked the company to discuss the impact of these imbalances in relevant baseline characteristics between the two arms on the results being derived from the APPEAR-C3G trial. In responding to the EAG’s request, the company provided

a response, and the company also performed post-hoc sensitivity analyses due to these imbalances. The EAG considered that the results of these post-hoc sensitivity analyses where these imbalanced baseline characteristics were adjusted for were generally consistent with the results of the primary analysis.

The EAG did not consider the inclusion of nine patients derived from three sites across the UK as constituting a meaningful representation of ‘*several UK study sites*’ or of a meaningful number of patients to justify supportive of generalisability. The EAG also notes that there are differences in characteristics between trial patients and those in *RaDaR* cohort, and while clinical opinion and advice is important and valid and has suggested the trial populations can be generalised, little evidence was presented to support such a generalisation.

3.2.5 External validity

The EAG has some concerns about the applicability and generalisability of the included trials to the relevant population in England and Wales. Primarily we do not think it clear as to whether the DP population includes both native and post-transplant C3G recurrence and the relevance and generalisability of the trial population to the clinical population of England and Wales is of limited evidence, with some differences in characteristics with the *RaDaR* cohort, and with minimal involvement of UK based sites (three) and participants (nine). Additionally, the EAG highlights that the DP excludes eculizumab on the basis that it is considered of minimal relevance as a comparator, however if recurrent C3G post-transplant patients were treated with current ECM then they might receive it. This uncertainty is obviously a concern. The EAG is of the position an ITC could have been performed to generate data relevant to this subpopulation.

EAG comment: Concerns exist around the relevance and generalisability of the included data to the clinical population in England and Wales, and particularly C3G post-transplant patients.

3.2.6 Efficacy results of the included studies

3.2.6.1 Primary efficacy results: proteinuria reduction

3.2.6.1.1 C_fB in 24-hour UPCR up to Month 6 (double-blind period)

The CS included the following statements: “*Iptacopan treatment resulted in a statistically significant and clinically meaningful relative reduction in 24h UPCR by 35.1% (95% CI: 13.8%, 51.1%; p=0.0014) following 6 months of treatment compared with placebo (both arms as add-on to background therapy)*”.¹ Further details can be found in Table 3.14.

Table 3.14: MMRM analysis of log-transformed ratio to baseline in 24-hour UPCR (g/g) up to Month 6 (FAS)

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus placebo		
					Geometric adjusted ratio (95% CI)	% Reduction (95% CI)	1-sided p-value
Day 90	Iptacopan	38	36	0.601 (0.493, 0.731)	0.603 (0.454, 0.800)	39.7 (20.0, 54.6)	-
	Placebo	36	35	0.996 (0.816, 1.217)			

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus placebo		
					Geometric adjusted ratio (95% CI)	% Reduction (95% CI)	1-sided p-value
Day 180	Iptacopan	38	36	0.698 (0.572, 0.852)	0.649 (0.489, 0.862)	35.1 (13.8, 51.1)	0.0014
	Placebo	36	36	1.076 (0.881, 1.313)			

Based on Table 10 of the CS.¹

b.i.d. = twice daily; CI = confidence interval; CS = company submission; FAS = full analysis set; MMRM = mixed model of repeated measures; N = number of all patients; UPCR = urine protein-to-creatinine ratio

3.2.6.1.2 Sensitivity analyses (double-blind period)

The company further explored the sensitivity analyses by considering the alternative imputation approaches following intercurrent events, where the company reported that, “*The sensitivity analyses are consistent with the primary analysis, confirming robustness to varying assumptions on the handling of intercurrent events.*”¹ Further details can be found in Table 3.15.

Table 3.15: Summary of sensitivity analyses for primary endpoint at Month 6 (FAS)

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		% Reduction (95% CI)	1-sided p-value
Pre-specified sensitivity analyses			
Log-transformed ratio to baseline in UPCR (sampled from 24-hour urine collection) at Month 6	Primary analysis: “Jump to reference” imputation approach following the intercurrent event ^a	35.1 (13.8, 51.1)	0.0014
	Sensitivity analysis 1: Imputation under the MAR assumption following the intercurrent event ^a	35.7 (14.7, 51.6)	0.0011
	Sensitivity analysis 2: “Copy-reference” imputation approach following the intercurrent event ^a	35.4 (14.3, 51.3)	0.0012
Post-hoc sensitivity analyses			
Log-transformed ratio to baseline in UPCR (sampled from 24-hour urine collection) at Month 6	Post-hoc sensitivity analysis 1: Adjustment for baseline eGFR (ml/min/1.73 m ²)	35.0 (13.4, 51.2)	0.0016
	Post-hoc sensitivity analysis 2: Adjustment for age group at C3G diagnosis ^b	35.8 (14.2, 52.0)	0.0014
	Post-hoc sensitivity analysis 3: Adjustment for C3G subtype at diagnosis ^c	38.4 (17.5, 54.1)	0.0006

Based on Table 11 of the CS¹

^a Hypothetical strategy was applied to handle intercurrent event of increasing corticosteroid dose (one event occurred at study Day 106 in the iptacopan group). Treatment policy strategy was applied to handle two intercurrent events of treatment discontinuation for all analyses.

^b Age group at C3G diagnosis was categorised as <18 years and ≥18 years.

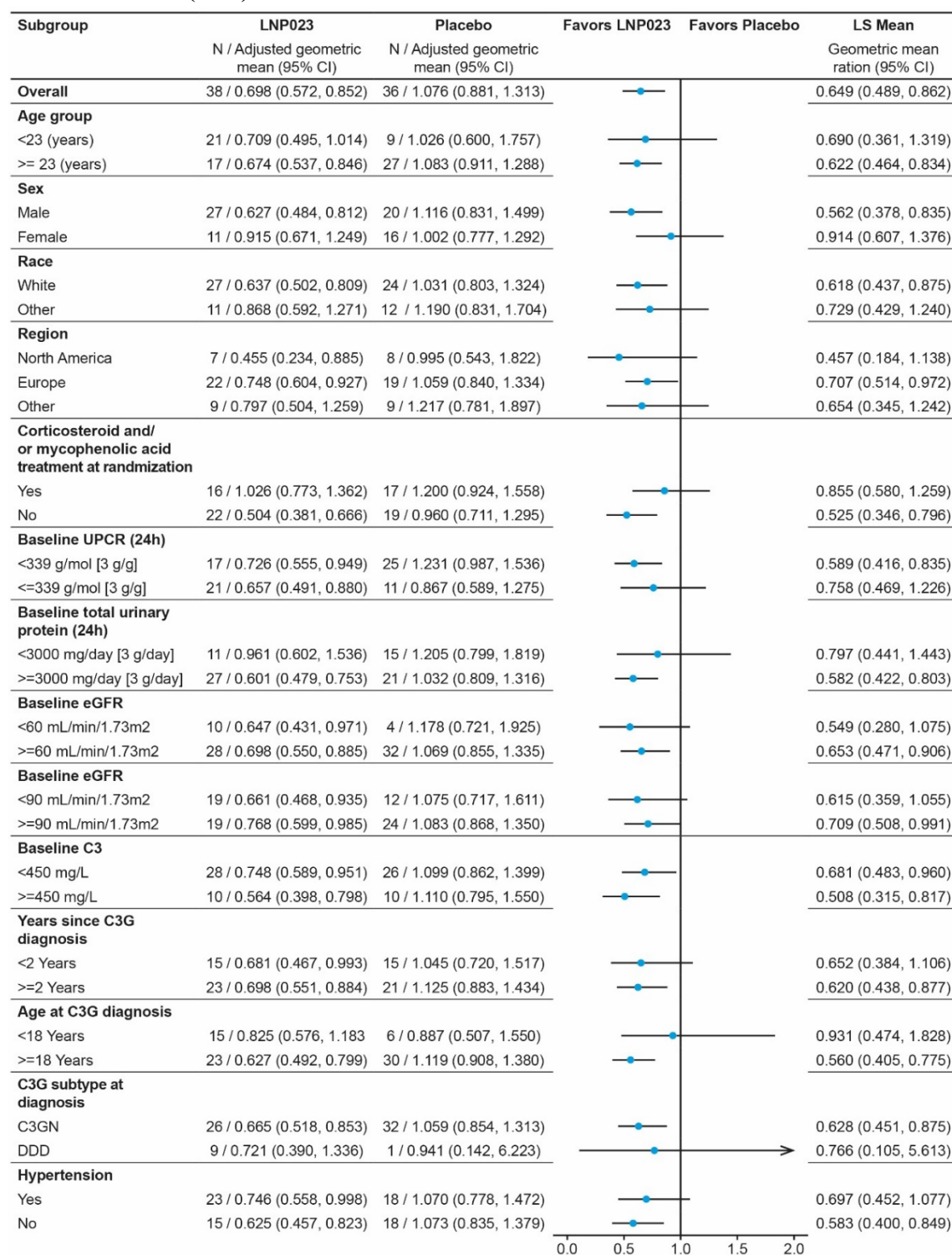
^c C3G subtype at diagnosis was categorised as C3GN and other.

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. versus placebo	
		% Reduction (95% CI)	1-sided p-value
b.i.d. = twice daily; C3G = complement 3 glomerulopathy; C3GN = complement 3 glomerulonephritis; CI = confidence interval; eGFR = estimated glomerular filtration rate; FAS = full analysis set; MAR = missing-at-random; UPCR = urine protein-to-creatinine ratio			

3.2.6.1.3 pre-specified subgroup analyses (double-blind period)

The company also conducted pre-specified subgroup analyses, where they reported that, “*Iptacopan consistently improved 24h UPCR at Day 180 versus placebo across subgroups, including demographics (such as age, sex, race) and baseline disease characteristics (including UPCR, eGFR, and C3G subtype).*”

The company also reported that “*due to the small sample size in the subgroups, the precision of the estimates is low, as indicated by wide confidence intervals for some subgroups.*”¹ Further details can be found in Figure 3.6.

Figure 3.6: Forest plot of subgroup analysis of log-transformed ratio to baseline in UPCR 24-hour at Month 6 (FAS)Based on Figure 8 of the CS¹

C3G = complement 3 glomerulopathy; C3GN = complement 3 glomerulonephritis; CS = company submission; DDD = dense deposit disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; FAS = full analysis set; LS = least squares; MMRM = mixed model for repeated measures; SAP = statistical analysis plan; UPCR = urine protein-to-creatinine ratio

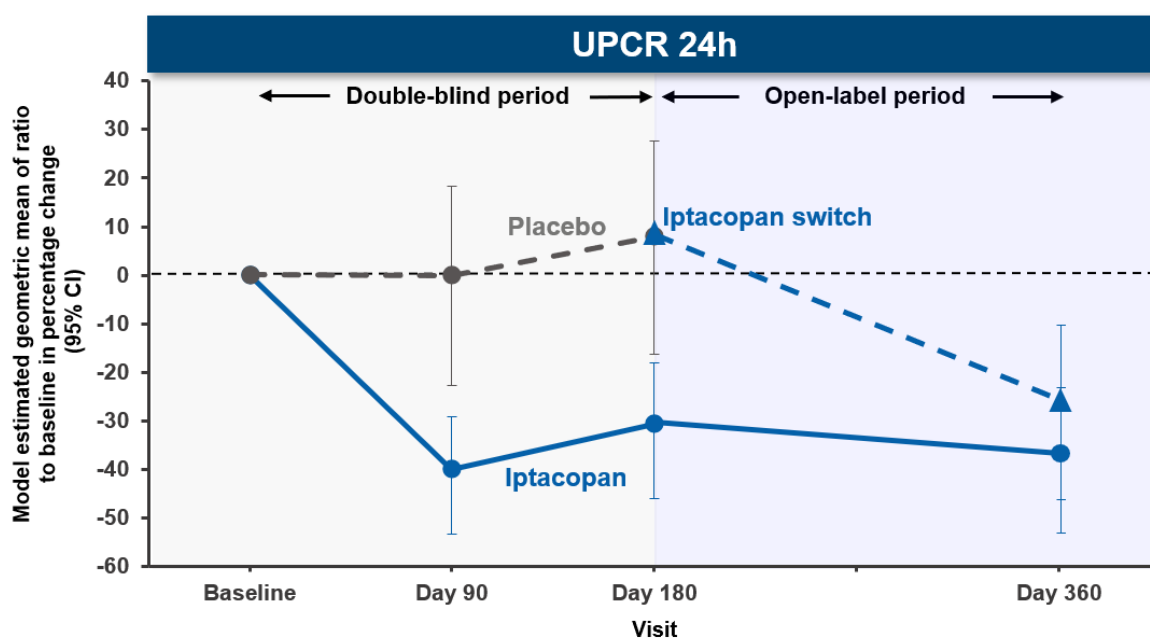
EAG comment: It appears that there was little difference in treatment effect between these subgroups being analysed.

3.2.6.1.4 CfB in 24h UPCR up to Month 12 (open-label period)

The company reported that “Results from the open-label period of APPEAR-C3G demonstrated that in patients initially randomised to iptacopan, the observed reduction in 24h UPCR was sustained up to Month 12 (40% geometric mean reduction from baseline; geometric mean ratio 0.60 [95% CI: 0.45, 0.80])”¹

The CS also included the following statements: “Patients initially randomised to the placebo arm who switched to open-label iptacopan at Month 6 had a 27% UPCR reduction from baseline to Month 12 (geometric mean ratio 0.73 [95% CI: 0.58, 0.92]). Considering the rise in UPCR between baseline and Month 6 (while on placebo), the reduction in UPCR from Month 6 to Month 12 (on iptacopan) was 31%, which was similar to the reduction observed in the iptacopan arm from baseline to Month 6 (34%).”¹ Further details can be found in Figure 3.7 and Table 3.16.

Figure 3.7: Geometric mean reduction in 24-hour UPCR from baseline up to Month 12 (FAS)



Based on Figure 9 of the CS¹

CI = confidence interval; CS = company submission; FAS = full analysis set; UPCR = urine protein-to-creatinine ratio

Table 3.16: Geometric mean ratio of CfB in 24-hour UPCR (g/g) up to Month 12 by treatment group (FAS)

Visits	Statistics	Iptacopan 200 mg b.i.d. (N=38)	Placebo-iptacopan switch ^a (N=36)
Day 90	Geometric mean ^b	0.56	1.00
	95% CI	0.45–0.71	0.83–1.20
Day 180 ^a	Geometric mean	0.66	1.09
	95% CI	0.51–0.85	0.92–1.28
Day 360	Geometric mean	0.60	0.73
	95% CI	0.45–0.80	0.58–0.92

Based on Table 12 of the CS.¹

^a The switch from placebo to iptacopan 200 mg b.i.d. took place following the Day 180 visit.

Visits	Statistics	Iptacopan 200 mg b.i.d. (N=38)	Placebo-iptacopan switch ^a (N=36)
^b Geometric mean was calculated by back transforming the mean of the log-transformed data. b.i.d. = twice daily; CfB = change from baseline; CI = confidence interval; CS = company submission; FAS = full analysis set; N = number of patients in the full analysis set; UPCR = urine protein-to-creatinine ratio			

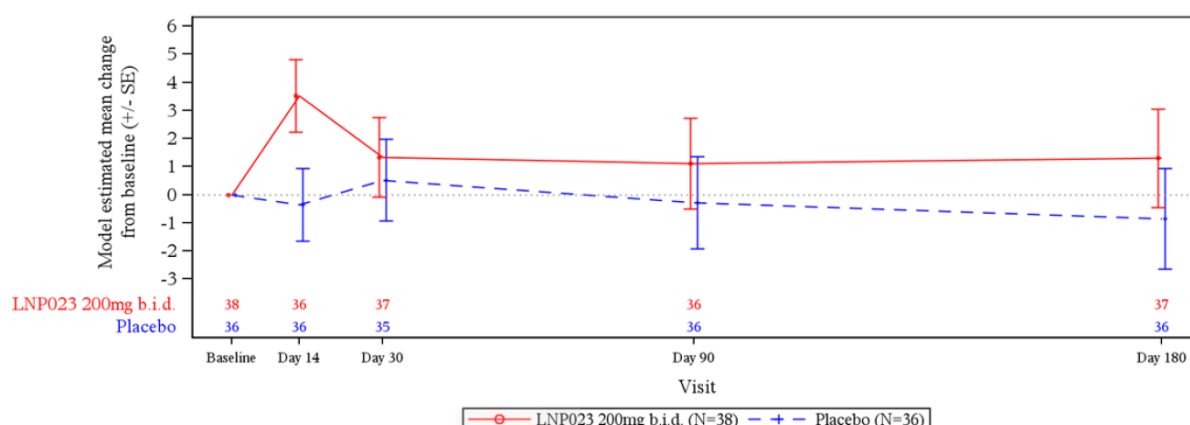
3.2.6.2 Secondary efficacy results: eGFR

3.2.6.2.1 CfB in eGFR up to Month 6

The CS included the following statements: “A numerical improvement in eGFR was observed in the iptacopan arm compared with the placebo arm at Month 6. At this time point the adjusted mean changes from baseline in eGFR (mL/min/1.73m²) in the iptacopan arm and the placebo arm were 1.30 (95% CI: -2.14, 4.73) and -0.86 (95% CI: -4.36, 2.64), respectively. The adjusted mean difference of iptacopan versus placebo was 2.16 mL/min/1.73m² (95% CI: -2.75, 7.06; multiplicity-adjusted 1-sided p-value: 0.3241).”¹ Further details can be found in Table 3.17.

The mean change in eGFR from baseline to 6 months for the two study arms is presented in Figure 3.8.

Figure 3.8: Mean change of eGFR from baseline up to Month 6 (FAS)



Source Based on Figure 11 of the CS.¹

b.i.d. = twice daily; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set; SE = standard error

Table 3.17: MMRM for CfB in eGFR (ml/min/1.73 m²) at Month 6 (FAS)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	Nominal 1-sided p-value
Day 180	Iptacopan	38	37	1.295 (-2.136, 4.726)	2.156 (-2.749, 7.061)	0.1945
	Placebo	36	36	-0.861 (-4.357, 2.635)		

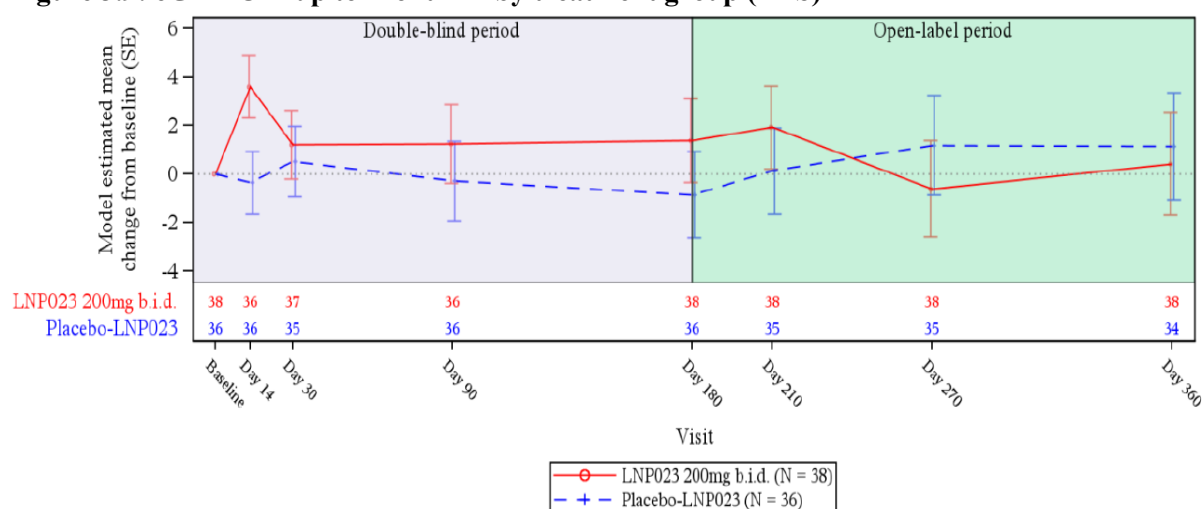
Based on Table 13 of the CS¹
b.i.d. = twice daily; CfB = change from baseline; CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set; MMRM = mixed model of repeated measures; N = total number of patients

3.2.6.2.2 CfB in eGFR up to Month 12

The CS included the following statements: “*Iptacopan treatment also numerically increased eGFR in the placebo-iptacopan switch arm after switching to iptacopan at the start of the open-label period.*”¹ Further details can be found in Figure 3.9.

The company also reported that “*The mean changes from baseline in eGFR in the iptacopan arm and the placebo-iptacopan switch arm were 0.44 mL/min/1.73m² (95% CI: -3.76, 4.64) and 1.15 mL/min/1.73m² (95% CI: -3.22, 5.53), respectively at Day 360.*”¹ Further details can be found in Table 3.18.

Figure 3.9: eGFR CfB up to Month 12 by treatment group (FAS)



Based on Figure 12 of the CS¹

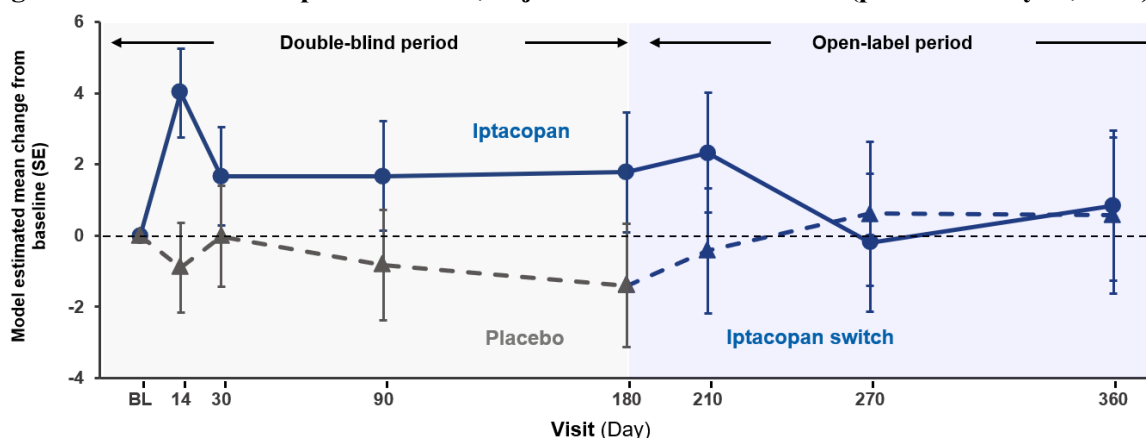
b.i.d. = twice daily; CfB = change from baseline; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set; N = number of participants in full analysis set; SE = standard error

Table 3.18: MMRM analysis of CfB in eGFR (mL/min/1.73 m²) up to Month 12 (FAS)

Visit	Treatment	N	n	Iptacopan 200 mg b.i.d. versus Placebo	
				Adjusted mean [SE] (95% CI)	Adjusted mean difference (95% CI)
Day 180	Iptacopan	38	38	1.382 [1.723] (-2.052, 4.817)	2.230 (-2.700, 7.160)
	Placebo	36	36	-0.848 [1.770] (-4.375, 2.680)	-
Day 360	Iptacopan	38	38	0.439 [2.106] (-3.762, 4.641)	-
	Placebo-iptacopan switch	36	34	1.152 [2.194] (-3.222, 5.526)	-

Source: Based on Table 14 of the CS.¹

b.i.d. = twice daily; CfB = change from baseline; CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set; I/C = intercurrent events; MMRM = mixed model of repeated measures; N = number of all patients included in the analysis (with non-missing baseline and covariates); n = number of patients with values non-missing and not imputed as per I/C handling strategy at designated visit; SE = standard error

Figure 3.10: eGFR CfB up to Month 12, adjusted for baseline UPCR (post hoc analysis; FAS)

Based on Figure 13 of the CS¹

CfB = change from baseline; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set; SE = standard error; UPCR = urine protein-to-creatinine ratio

Table 3.19: MMRM analysis of CfB in eGFR (ml/min/1.73 m²) up to Month 12, adjusted for baseline UPCR (post hoc analysis; FAS)

Visit	Treatment	N	n	Iptacopan 200 mg b.i.d. versus Placebo	
				Adjusted mean [SE] (95% CI)	Adjusted mean difference (95% CI)
Day 180	Iptacopan	38	38	1.787 [1.683] (-1.568, 5.141)	3.185 (-1.657, 8.028)
	Placebo	36	36	-1.399 [1.733] (-4.852, 2.055)	-
Day 360	Iptacopan	38	38	0.844 [2.107] (-3.360, 5.048)	-
	Placebo-iptacopan switch	36	34	0.572 [2.199] (-3.814, 4.957)	-

Based on Table 15 of the CS¹

b.i.d. = twice daily; CfB = change from baseline; CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set; MMRM = mixed model of repeated measures; N = number of all participants included in the analysis (with non-missing baseline and covariates); n = number of participants with values non-missing and non-missing baseline at the designated visit; SE = standard error; UPCR = urine protein-to-creatinine ratio

The EAG noted that there was a big increase in CfB of eGFR at Day 14 for the iptacopan arm of the APPEAR-C3G trial. The EAG asked the company to provide an explanation for this big increase in CfB of eGFR at Day 14 for the iptacopan arm of the APPEAR-C3G. In responding to the EAG's request, the company provided the following response:

- *“C3G patients experience overactivation of the complement alternative pathway which leads to deposition of complement component 3 (C3) within the glomeruli, triggering inflammation. Two UK clinicians consulted on a call to obtain clinical expert input for Novartis' response to the EAG's clarification questions assumed that the numerical increase in eGFR at Day 14 following iptacopan initiation is due to the rapid resolution of the intense inflammation in the kidney of C3G patients through alternative pathway inhibition.*
- *The increase in eGFR on Day 14 of iptacopan treatment was transient and short-term, with the Day 30 mean eGFR value on a similar level as subsequent measurements.”*

The company further provided a sensitivity analysis on eGFR slope which excluded the data of Day 14 measurements (see Table 3.20 below).

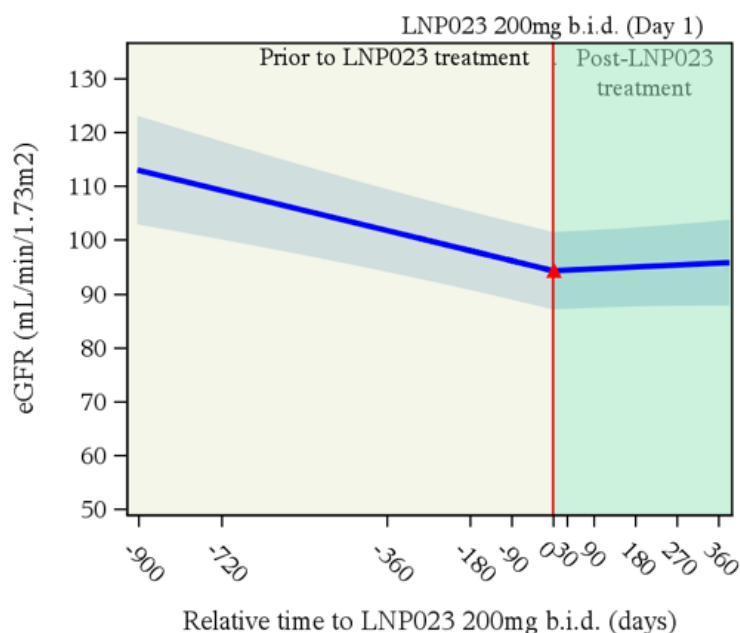
Table 3.20: APPEAR-C3G eGFR slope sensitivity analysis excluding Day 14 measurements

Analysis	Annual eGFR slope, mL/min/1.73 m ² /year (95% CI)		
	SoC	Iptacopan	Iptacopan treatment effect
Base-case analysis (N=74) SoC: pre-iptacopan data, up to 2.5 years Iptacopan: on-iptacopan data, up to 2 years treatment duration	-7.224 (-10.101, -4.348)	-0.289 (-3.884, 3.305)	6.935 (3.481, 10.390)
Sensitivity analysis excluding Day 14 measurements (N=74) SoC: pre-iptacopan data, up to 2.5 years Iptacopan: on-iptacopan data, up to 2 years treatment duration			
Based on Table 4 of the company clarification response ⁴ C3G = complement 3 glomerulopathy; CI = confidence interval; eGFR = estimated glomerular filtration rate; SoC = standard of care			

EAG comment: Given that there was a big increase in C_fB of eGFR at Day 14 for the iptacopan arm of the APPEAR-C3G trial, the EAG asked the company to provide an explanation for this big increase. In responding to the EAG's request, the company provided a response in the company's clarification response file. The EAG considered the company's explanation which appears to be reasonable. The results of the sensitivity analysis where the data of Day 14 measurements were excluded showed that the short-term and temporary increase in mean eGFR at the start of iptacopan treatment of the iptacopan arm did not have a major impact on the longer-term eGFR slope estimates.

3.2.6.2.3 eGFR slope change analyses

The company reported that “The mean pre-iptacopan eGFR slope was $-7.57 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $-10.57, -4.56$) in the full study population. Initiation of iptacopan led to stabilisation of eGFR, with eGFR slope for iptacopan estimated as $1.44 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $-2.18, 5.06$), which equated to a change in eGFR slope of $9.01 \text{ mL/min/1.73 m}^2/\text{year}$ (95% CI: $5.43, 12.60$; $p < 0.0001$) compared to the pre-iptacopan eGFR decline.” Further details can be found in Figure 3.11.

Figure 3.11: eGFR slope change with iptacopan treatment – APPEAR-C3G (n=74) (FAS)

Based on Figure 14 of the CS¹

b.i.d. = twice daily; C3G = complement 3 glomerulopathy; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set

In terms of eGFR slope change with iptacopan treatment, the EAG asked the company to provide a separate analysis for the double-blind period of the APPEAR-C3G trial as well as a separate analysis for the open-label period of the APPEAR-C3G trial. In responding to the EAG's request, the company provided the results of separate analysis for the double-blind period of the APPEAR-C3G trial as well as a separate analysis for the open-label period of the APPEAR-C3G trial. Table 3.21 presents the results of estimated eGFR (ml/min/1.73 m²) slopes per year by study arm and treatment period.

Table 3.21: Model estimated eGFR (ml/min/1.73 m²) slopes per year by study arm and treatment period (FAS)

	Pre-randomisation period	Double-blind treatment period		Open-label treatment period*	
Study arm	eGFR slope per year (95% CI)	Study treatment	eGFR slope per year (95% CI)	Study treatment	eGFR slope per year (95% CI)
Iptacopan (N=38)	-10.753 (-15.510, -5.996)	Iptacopan	-0.025 (-6.929, 6.878)	Iptacopan	[REDACTED]
Placebo (N=36)	-7.641 (-12.279, -3.003)	Placebo	-3.079 (-10.131, 3.973)	Iptacopan	[REDACTED]
All patients (N=74)	-	-	-	Iptacopan	[REDACTED]

Based on Table 5 of the company clarification response⁴

* eGFR slopes for open-label period were estimated in a separate model. eGFR slopes per year were analysed using a linear mixed effects model including treatment as a factor, time (analysis day before or day after study Day 1) as a continuous covariate, treatment*time as a fixed effect, participant-level intercept and slope (time) as random effects. Intercurrent events were handled with a treatment policy strategy.

CI = confidence interval; eGFR = estimated glomerular filtration rate; FAS = full analysis set; N = number of all patients included in the analysis

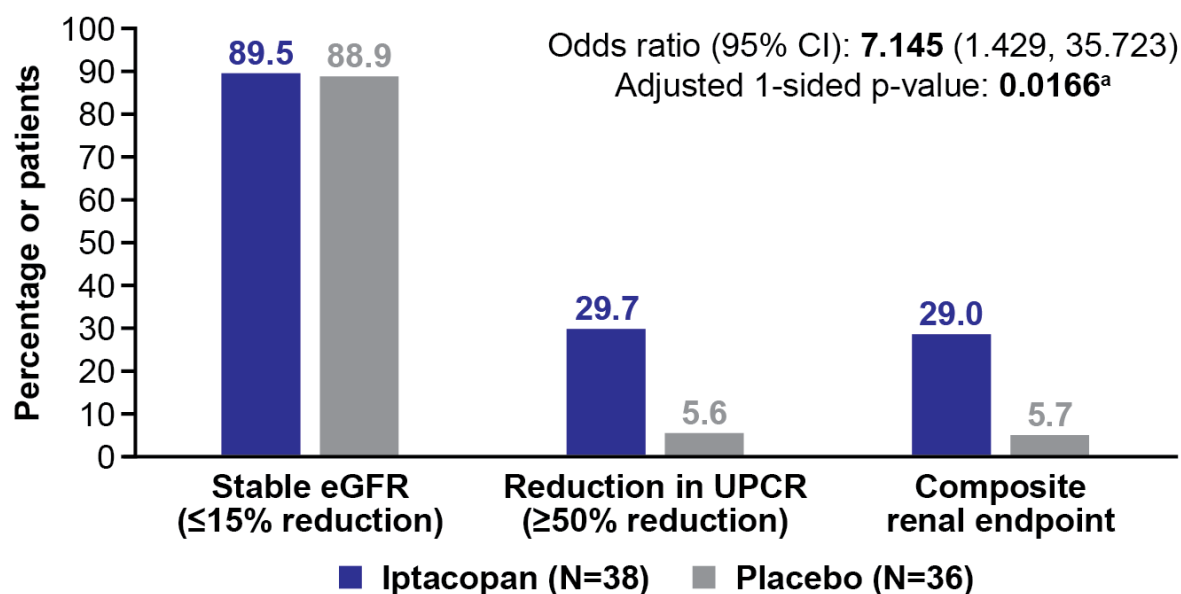
EAG comment: For the eGFR slope change with iptacopan treatment, the EAG asked the company to provide a separate analysis for the double-blind period of the APPEAR-C3G trial as well as a separate analysis for the open-label period of the APPEAR-C3G trial. In responding to the EAG's request, the company provided the results of separate analysis for the double-blind period of the APPEAR-C3G trial as well as a separate analysis for the open-label period of the APPEAR-C3G trial. These results showed that there were variations in the slope change in the iptacopan treatment arm between double-blind treatment period and open-label treatment.

3.2.6.3 Secondary efficacy results: composite renal endpoint

3.2.6.3.1 Composite renal endpoint at Month 6

In Section 2.4.3.3, the company stated that “Results from APPEAR-C3G demonstrated a statistically significant improvement in the proportion of participants achieving the composite endpoint of stable eGFR ($\leq 15\%$ decrease) and $\geq 50\%$ reduction in UPCR at Month 6 in patients treated with iptacopan versus placebo (multiplicity adjusted 1-sided $p=0.0166$). The marginal proportion of participants (95% CI) who achieved the composite renal endpoint at Month 6 was 29.0% (14.9%, 43.1%) in the iptacopan arm and 5.7% (–1.9%, 13.4%) in the placebo arm.”¹ Further details can be found in Figure 3.12.

Figure 3.12: Marginal proportion of patients who achieved composite renal endpoint at Month 6 ($\leq 15\%$ reduction in eGFR + $\geq 50\%$ reduction in UPCR; FAS)



Based on Figure 16 of the CS¹

^a Statistically significant after adjustment for multiple testing.

CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set; N = number of all patients included in the analysis (with non-missing baseline and covariates); UPCR = urine protein-to-creatinine ratio

3.2.6.3.2 Composite renal endpoint up to Month 12

The company reported that “The marginal proportion (95% CI) of participants who achieved the composite renal endpoint at Day 360 was 44.1% (28.9%, 59.4%) in participants randomised to the iptacopan arm, and 24.0% (9.9%, 38.1%) in participants randomised to the placebo arm who had switched to iptacopan at the start of the open-label period.”¹ Further details can be found in Table 3.22.

Table 3.22: Logistic regression of proportion of patients who achieved composite renal endpoint up to Month 12 (FAS)

Visit	Treatment	N	Stable eGFR (≤15% reduction) n/M (%)	Reduction in proteinuria (≥50% reduction) n/M (%)	Composite renal endpoint n/M ^a (%)	Marginal proportion (95% CI)	Difference in marginal proportions (95% CI) iptacopan versus placebo	OR (95% CI)
Day 180	Iptacopan	38	34/38 (89.5)	11/37 (29.7)	11/37 (29.7)	0.290 (0.149, 0.431)	0.233 (0.072, 0.394)	7.145 (1.429, 35.723)
	Placebo	36	32/36 (88.9)	2/36 (5.6)	2/36 (5.6)	0.057 (-0.019, 0.134) ^b	-	-
Day 360	Iptacopan	38	32/38 (84.2)	17/37 (45.9)	17/38 (44.7)	0.441 (0.289, 0.594)	-	-
	Placebo-iptacopan switch	36	30/34 (88.2)	10/34 (29.4)	8/34 (23.5)	0.240 (0.099, 0.381)	-	-

Based on Table 17 of the CS¹^a Considering the initiation or intensification of antiproteinuric therapies or KRT as treatment failures.^b The lower bound of the CI is negative due to a low proportion of placebo patients achieved the composite renal endpoint.

CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate; FAS = full analysis set; KRT = kidney replacement therapy; M = number of patients with non-missing response variable at designated visit; N = number of all patients in the full analysis set; n = number of patients who reached the endpoint at designated visit; OR = odds ratio

3.2.6.4 Secondary efficacy results: C3G histologic total activity score**3.2.6.4.1 CfB in C3G histologic total activity score at Month 6**

The company reported that “No significant differences were observed in the histologic total activity score from kidney biopsies after 6 months of iptacopan treatment in comparison with placebo. Treatment with iptacopan decreased the C3G histologic total activity score by an adjusted mean of -1.95 (95% CI: $-2.69, -1.20$); in the placebo arm, an adjusted mean decrease of -1.11 (95% CI: $-1.83, -0.39$) was observed, resulting in a non-statistically significant difference.”¹ Further details can be found in Table 3.23.

Table 3.23: CfB in histologic total activity score at Month 6 (FAS)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	1-sided p-value
Day 180	Iptacopan	37	32	-1.946 ($-2.691, -1.201$)	-0.833 ($-1.872, 0.205$)	0.0579

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	1-sided p- value
	Placebo	36	34	-1.113 (1.831, -0.394)	-	-

Based on Table 18 of the CS¹
b.i.d. = twice daily; CfB = change from baseline; CI = confidence interval; CS = company submission; FAS = full analysis set; I/C = intercurrent event; n = number of participants with values non-missing and not imputed as per the I/C handling strategy at designated visit; N = number of all patients included in the analysis (with non-missing baseline and covariates)

3.2.6.4.2 CfB in C3G histologic total activity score at Month 12

The CS included the following statements: “Only two patients from the iptacopan arm and four patients from the placebo-iptacopan switch arm had evaluable kidney biopsies at the end of the open-label period, as kidney biopsies were not mandatory at Month 12. In the two patients randomised to the iptacopan arm, the mean change in histologic total activity score from baseline to Month 12 was -2.0 (SD: 2.83). In the four patients randomised to the placebo-iptacopan switch arm, the mean change in histologic total activity score from Month 6 to Month 12 (during open-label treatment with iptacopan) was -1.5 (SD: 1.9).”¹

3.2.6.5 Secondary efficacy results: FACIT-Fatigue total score

3.2.6.5.1 CfB in FACIT-Fatigue at Month 6

The company reported that “Mean (SD) FACIT-Fatigue scores at baseline were near the general population norm for both treatment arms: 42.4 (10.08) in the iptacopan arm and 41.9 (8.91) in the placebo arm.”¹

The company further demonstrated that “Participants taking iptacopan did not show an improvement in FACIT-Fatigue. The adjusted mean difference of CfB in the FACIT-Fatigue total score in the iptacopan arm versus placebo arm was -2.60 (95% CI: -6.03, 0.84; multiplicity-adjusted 1-sided p-value: 0.9310) after 6 months of treatment.”¹ Further details can be found in Table 3.24.

Table 3.24: MMRM analysis of CfB in FACIT-Fatigue total score at Month 6 (FAS)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	1-sided p- value
Day 180	Iptacopan	36	35	-0.410 (-2.755, 1.935)	-2.598 (-6.032, 0.835)	0.9310
	Placebo	31	31	2.188 (-0.334, 4.711)	-	-

Based on Table 19 of the CS¹
b.i.d. = twice daily; CfB = change from baseline; CI = confidence interval; CS = company submission; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FAS = full analysis set; I/C = intercurrent event; MMRM = mixed model of repeated measures; n = number of participants with values non-missing and not imputed as per the I/C handling strategy at designated visit; N = number of all patients included in the analysis (with non-missing baseline and covariates)

3.2.6.5.2 CfB in FACIT-Fatigue at Month 12

The company reported that “At Month 12, the adjusted mean changes from baseline in the FACIT-Fatigue total score in the iptacopan and placebo-iptacopan switch arms were -0.78 (95% CI: $-3.18, 1.63$) and 2.72 (95% CI: $0.07, 5.37$), respectively.”¹

3.2.6.6 Exploratory efficacy results: glomerular C3 deposit scores

The company reported that “Treatment with iptacopan reduced glomerular C3 deposition in kidney biopsies, as measured by the adjusted mean difference in C3 deposit score between iptacopan versus placebo at Month 6 (-1.88 [95% CI: $-3.30, -0.45$]; 1-sided $p=0.0053$).”¹ Further details can be found in Table 3.25.

Table 3.25: CfB in glomerular C3 deposit scores at Month 6 (FAS)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus Placebo	
					Adjusted mean difference (95% CI)	1-sided p-value
Day 180	Iptacopan	35	32	-0.781 ($-1.811, 0.250$)	-1.875 ($-3.298, -0.452$)	0.0053
	Placebo	36	35	1.094 ($0.111, 2.078$)	-	-

Based on Table 20 of the CS¹
b.i.d. = twice daily; C3 = complement component 3; CfB = change from baseline; CI = confidence interval; CS = company submission; FAS = full analysis set; n = number of participants with values non-missing at designated visit; N = number of all patients included in the analysis (with non-missing baseline and covariates)

3.2.6.7 Exploratory efficacy results: effect of iptacopan on complement biomarkers

The company reported that “With iptacopan treatment, there was a rapid rise in serum C3 levels, which was sustained throughout the study, while the C3 concentration in the placebo arm remained unchanged. In addition, decreases were observed with iptacopan in alternative pathway activity, plasma Bb, plasma sC5b-9 and urinary sC5b-9. Circulating biomarker levels were measured up to Month 12, to demonstrate the change in inhibition of the complement pathway following initiation of iptacopan treatment in the placebo-iptacopan switch arm. A sustained increase of serum C3 in the iptacopan arm was observed for the entire 12 months treatment period, as well as a rapid rise in placebo arm patients after switching to iptacopan at Day 180, mirroring the effect seen in the iptacopan arm in the double-blind period.”¹ Further details can be found in Table 3.26.

Table 3.26: Circulating biomarker levels up to Month 12 (FAS)

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus placebo
					% change (95% CI)
Serum C3					
Day 180	Iptacopan	38	38	2.853 (2.383, 3.416)	177.1 (114.1, 258.6)
	Placebo	36	36	1.030 (0.856, 1.238)	
Day 360	Iptacopan	38	38	3.107 (2.724, 3.543)	N/A
	Placebo-iptacopan switch	36	34	3.003 (2.622, 3.440)	

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. versus placebo
					% change (95% CI)
Alternative pathway activity (serum Wieslab assay [%]) ^a					
Day 180	Iptacopan	31	31	0.627 (0.516, 0.760)	−40.1 (−54.0, 21.8)
	Placebo	35	35	1.045 (0.871, 1.254)	
Day 360	Iptacopan	31	31	0.573 (0.539, 0.609)	N/A
	Placebo-iptacopan switch	35	33	0.604 (0.570, 0.640)	
Plasma Bb (ng/ml)					
Day 180	Iptacopan	31	31	0.951 (0.865,1.046)	−3.9 (−15.9, 9.9)
	Placebo	35	35	0.989 (0.905,1.082)	
Day 360	Iptacopan	31	31	1.062 (0.935,1.206)	N/A
	Placebo-iptacopan switch	35	35	1.126 (0.998,1.272)	
Plasma sC5b-9 (ng/ml)					
Day 180	Iptacopan	31	31	0.326 (0.270, 0.393)	−66.4 (−74.0, −56.6)
	Placebo	35	35	0.972 (0.815, 1.158)	
Day 360	Iptacopan	31	31	0.335 (0.279, 0.403)	N/A
	Placebo-iptacopan switch	35	33	0.339 (0.284, 0.405)	
Urinary sC5b-9/creatinine (pg/nmol)					
Day 180	Iptacopan	31	31	0.120 (0.072, 0.199)	−81.6 (−91.0, −62.3)
	Placebo	32	32	0.648 (0.392, 1.071)	
Day 360	Iptacopan	31	30	0.164 (0.093, 0.287)	N/A
	Placebo-iptacopan switch	32	30	0.148 (0.085, 0.259)	
Based on Table 20 of the CS ¹					
^a Proportion of values outside limits of quantification >20% for both treatment groups at all visits, model estimates may be biased.					
Bb = cleaved Factor B; b.i.d. = twice daily; C3 = complement component 3; C5b-9 = complement 5b-9 complex; CI = confidence interval; CS = company submission; FAS = full analysis set; n = number of patients with values non-missing and non-missing baseline at the designated visit; N = number of all patients included in the analysis (with non-missing baseline and covariates); N/A = not applicable					

3.2.7 Adverse events

The safety sets presented in this Section are shown below:¹

- The controlled safety set (N=74) includes data from the 6-month double-blind placebo-controlled period of APPEAR-C3G from all adult patients who received at least one dose of iptacopan 200 mg b.i.d. (N=38) or placebo (N=36)
- The broad safety set (N=101) includes data from all adult patients who received at least one dose of iptacopan 200 mg b.i.d. in the treatment period of any of the three iptacopan studies in C3G (Phase 2, APPEAR-C3G, and the ongoing open-label extension study), up to the data cut-off date of 6 May 2024.

3.2.7.1 Summary of adverse events

A summary of AEs for both the controlled safety set and the broad safety set is presented in Table 3.27.

Table 3.27: Summary of AEs in controlled safety set and broad safety set

	Controlled safety set		Broad safety set
	Iptacopan 200 mg b.i.d. (N=38)	Placebo (N=36)	Iptacopan 200 mg b.i.d. (N=101)
Number of patients, n (%)			
TEAEs	30 (78.9)	24 (66.7)	86 (85.1)
TEAEs suspected to be related to study treatment	7 (18.4)	4 (11.1)	23 (22.8)
SAEs	3 (7.9)	1 (2.8)	20 (19.8)
SAEs suspected to be treatment-related	1 (2.6)	0	4 (4.0)
Severe AEs	2 (5.3)	1 (2.8)	12 (11.9)
Deaths	0	0	1 (1.0)
Treatment discontinuations due to AEs	0	0	3 (3.0)
Dose reductions or interruptions due to AEs	4 (10.5)	4 (11.1)	11 (10.9)
Based on Table 25 of the CS ¹ AE = adverse event; b.i.d. = twice daily; CS = company submission; n = number of patients with at least one event; SAE = serious adverse event; TEAE = treatment-emergent adverse event			

3.2.7.2 Treatment-emergent adverse events

The company reported that “*The total incidence of TEAEs during the double-blind phase in patients treated with iptacopan was 78.9%, compared with 66.7% among patients receiving placebo. The incidence of TEAEs in the broad safety set was 85.1%.*”¹ Further details can be found in Table 3.28.

The company further reported that “*In the controlled safety set, TEAEs suspected to be treatment-related were reported by the investigator in 18.4% and 11.1% of patients in the iptacopan and placebo groups, respectively. In the broad safety set, TEAEs suspected to be treatment-related were reported by the investigator in 22.8% of patients.*”¹ Further details can be found in Table 3.29.

Table 3.28: Summary of TEAEs (≥5% in any treatment group)

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients, n (%)			
Number of patients with at least one event	30 (78.9)	24 (66.7)	86 (85.1)
COVID-19	8 (21.1)	6 (16.7)	30 (29.7)
Blood creatine phosphokinase increased	5 (13.2)	1 (2.8)	11 (10.9)
Nasopharyngitis	4 (10.5)	1 (2.8)	14 (13.9)
Headache	2 (5.3)	1 (2.8)	9 (8.9)
Cough	2 (5.3)	1 (2.8)	8 (7.9)
Anaemia	2 (5.3)	0	6 (5.9)

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Upper respiratory tract infection	2 (5.3)	0	6 (5.9)
Blood creatinine increased	2 (5.3)	0	5 (5.0)
Otitis media	2 (5.3)	0	5 (5.0)
Aspartate aminotransferase increased	2 (5.3)	0	3 (3.0)
Respiratory tract infection viral	2 (5.3)	0	3 (3.0)
Vomiting	1 (2.6)	1 (2.8)	8 (7.9)
Diarrhoea	1 (2.6)	0	7 (6.9)
Hyperkalaemia	1 (2.6)	0	6 (5.9)
Nausea	1 (2.6)	2 (5.6)	4 (4.0)
Hypercholesterolaemia	1 (2.6)	2 (5.6)	3 (3.0)
Renal impairment	0	0	6 (5.9)
Vitamin D deficiency	0	1 (2.8)	6 (5.9)
Based on Table 26 of the CS ¹ COVID-19 = coronavirus disease 2019; CS = company submission; n = number of patients with at least one event; TEAE = treatment emergent adverse event			

Table 3.29: Summary of TEAEs suspected to be treatment-related

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients, n (%)			
Number of patients with at least one event	7 (18.4)	4 (11.1)	23 (22.8)
Blood creatine phosphokinase increased	1 (2.6)	0	2 (2.0)
Nausea	1 (2.6)	1 (2.8)	2 (2.0)
Aspartate aminotransferase increased	1 (2.6)	0	1 (1.0)
Blood culture positive	1 (2.6)	0	1 (1.0)
Cough	1 (2.6)	0	1 (1.0)
Dihydrotestosterone decreased	1 (2.6)	0	1 (1.0)
Headache	1 (2.6)	0	1 (1.0)
Lower respiratory tract infection	1 (2.6)	0	1 (1.0)
Otitis media	1 (2.6)	0	1 (1.0)
Pneumonia	1 (2.6)	0	1 (1.0)
Upper respiratory tract infection	1 (2.6)	0	1 (1.0)
Urinary tract infection	0	0	3 (3.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Abdominal pain	0	0	1 (1.0)
Acne	0	0	1 (1.0)
Acute respiratory distress syndrome	0	0	1 (1.0)
Adverse drug reaction	0	0	1 (1.0)

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Based on Table 27 of the CS ¹ CS = company submission; TEAE = treatment emergent adverse event			

3.2.7.3 Serious adverse events

The CS included the following statements that “*In the controlled safety set, SAEs were reported for three patients in the iptacopan group and one patient in the placebo group. In the broad safety set, SAEs were reported in 20 (19.8%) patients treated with iptacopan, who experienced a total of 36 SAEs. Approximately half of SAEs were infection related.*”¹ Further details can be found in Table 3.30.

The company further explained that “*In the controlled safety set, SAEs suspected to be treatment-related were reported in 2.6% and 0% of patients in the iptacopan and placebo groups, respectively. In the broad safety set, 9 SAEs suspected to be related to iptacopan treatment were reported in 4 patients (4.0% of 101 patients). Most treatment-related SAEs were infections, all of which were resolved or resolving at the time of data read-out.*”¹ Further details can be found in Table 3.31.

Table 3.30: All SAEs reported

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients, n (%)			
Number of patients with at least one event	3 (7.9)	1 (2.8)	20 (19.8)
Blood culture positive ^a	1 (2.6)	0	1 (1.0)
Chest discomfort	1 (2.6)	0	1 (1.0)
Infected bite	1 (2.6)	0	1 (1.0)
Acute kidney injury	0	1 (2.8)	3 (3.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Acute left ventricular failure	0	0	1 (1.0)
Acute respiratory distress syndrome	0	0	1 (1.0)
Appendicitis	0	0	1 (1.0)
Arrhythmia	0	0	1 (1.0)
Atrial fibrillation	0	0	1 (1.0)
C3 glomerulopathy	0	0	1 (1.0)
Cardiac failure	0	0	1 (1.0)
Drug abuse	0	0	1 (1.0)
Enteritis	0	0	1 (1.0)
Gastroenteritis	0	0	1 (1.0)
Hyperkalaemia	0	0	1 (1.0)
Intervertebral discitis	0	0	1 (1.0)
Mallory-Weiss syndrome	0	0	1 (1.0)
Norovirus infection	0	0	1 (1.0)
Overdose	0	0	1 (1.0)

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Pelvic inflammatory disease	0	0	1 (1.0)
Pericarditis	0	0	1 (1.0)
Pneumococcal sepsis	0	0	1 (1.0)
Pneumocystis jirovecii pneumonia	0	0	1 (1.0)
Pneumonia	0	0	1 (1.0)
Pyelonephritis	0	0	1 (1.0)
Renal impairment	0	0	1 (1.0)
Retroperitoneal haematoma	0	0	1 (1.0)
Septic shock	0	0	1 (1.0)
Streptococcal bacteraemia	0	0	1 (1.0)
Tendon rupture	0	0	1 (1.0)
Upper gastrointestinal haemorrhage	0	0	1 (1.0)
Ascites	0	1 (2.8)	0
Based on Table 28 of the CS ¹ C3 = complement component 3; CS = company submission = number of patients with at least one event; SAE = serious adverse event			

Table 3.31: Summary of SAEs suspected to be treatment-related

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients, n (%)			
Number of patients with at least one event	1 (2.6)	0	4 (4.0)
Blood culture positive ^a	1 (2.6)	0	1 (1.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Acute respiratory distress syndrome	0	0	1 (1.0)
Norovirus infection	0	0	1 (1.0)
Pneumococcal sepsis	0	0	1 (1.0)
Pneumocystis jiroveci pneumonia	0	0	1 (1.0)
Septic shock	0	0	1 (1.0)
Streptococcal bacteraemia	0	0	1 (1.0)
Based on Table 29 of the CS ¹ ^a Blood culture positive for Streptococcus pneumoniae. CS = company submission; n = number of patients with at least one event; SAE = serious adverse event			

EAG comment: As the company stated that approximately half of the serious adverse events (SAEs) were infection-related, the EAG asked the company to provide a detailed breakdown of the types and severity of infections observed (e.g., bacterial, viral or fungal) and also clarify any of these infections related to encapsulated bacteria (e.g., *Neisseria meningitidis*, *Streptococcus pneumoniae*). The company replied that “Most infections were non-serious and assessed by the investigator as not related to iptacopan.” As requested, the company also provided the types of infections reported across the C3G studies with ten patients experienced a total of 17 infection-related SAEs on iptacopan in the broad

safety set. Further details can be found in Table 3.32 below. The company further stated that, “Six of the below SAEs were related to encapsulated bacteria, occurring in a total of four patients. In all cases these were caused by streptococcal infections, with one patient experiencing *Streptococcus gallolyticus* infection (intervertebral discitis), and all others experiencing *Streptococcus pneumoniae* infections. The severity of these SAEs was moderate for two patients and severe for two patients.”⁴

Table 3.32: Infection SAEs reported across C3G studies (broad safety set)

Type of infection Number of SAEs	Severity			Total
	Mild	Moderate	Severe	
Bacterial (encapsulated)	0	4	2	6
Intervertebral discitis		1		1
Pneumonia pneumococcal		1	1	2
Pneumococcal sepsis		1		1
Septic shock			1	1
Streptococcal bacteraemia (evolved to septic shock)		1		1
Bacterial (other)	2	3	0	5
Appendicitis	1			1
Pelvic inflammatory disease		1		1
Pneumonia	1			1
<i>Pneumocystis jiroveci</i> pneumonia		1		1
Pyelonephritis		1		1
Bacterial/viral			1	1
Blood culture positive			1	1
Viral		1		1
Norovirus infection		1		1
Viral (probable)			1	1
Pericarditis			1	1
NR	1	2		3
Enteritis		1		1
Gastroenteritis	1			1
Infected bite		1		1
Total	3	10	4	17
Based on Table 10 of the company clarification response ⁴ C3G = complement 3 glomerulopathy; NR = not reported; SAEs = serious adverse events				

3.2.7.4 Deaths

The company reported that “One death occurred across the three C3G studies, during the open-label extension study. The cause of death was presumed to be cardiac arrhythmia that the investigator did not consider to be related to iptacopan.”¹

EAG comment: The company was asked to clarify the details of the one death and clarify any cardiovascular (CV) events reported, given the potential link between complement inhibition (or lack of it) and thrombosis. The company detailed that “A 24-year-old patient, originally in the Phase 2 Study, was found unresponsive and declared dead on Day 501. Post-mortem examination revealed no obvious

cause of death. The evidence pointing to cardiac arrhythmia included arteriolar-nephrosclerosis, a clinical history of C3G, hypertension, focal myocardial scar, and a clinical history of hypocalcaemia. The patient had pre-existing conditions including anxiety, palpitations, and hyperparathyroidism. Possible confounders for the event included concomitant medications of methylphenidate (potential adverse drug reactions [ADRs] of tachycardia and arrhythmia), venlafaxine (potential ADRs of tachycardia and arrhythmia) as well as trazodone (warning for QT prolongation).”

The company also provided the details of the CV events in the broad safety set in the iptacopan clinical trials in C3G, in Table 3.33 below. The company further stated that “across the clinical studies included in the marketing authorisation application for iptacopan in its first indication (paroxysmal nocturnal haemoglobinuria [PNH]), no clinically meaningful abnormalities in cardiac safety-related assessments were observed.”⁴

Table 3.33: Cardiovascular events (broad safety set)

Table 11: Summary of adverse events (broad safety set)			
Event	Number of patients in the broad safety set (N=101)	Severity	Relationship to iptacopan
SAEs			Not suspected to be related to iptacopan
Acute left ventricular failure	1	Moderate	
Atrial fibrillation	1	Moderate	
Pericarditis	1	Severe	
Cardiac failure	1	Moderate	
AEs			
Cardiomyopathy	1	Non-serious	
Based on Table 11 of the company clarification response ⁴ AE = adverse event; SAE = serious adverse event			

3.2.7.5 Treatment discontinuations due to AEs

The company reported that “No treatment discontinuations due to TEAEs were reported in the controlled safety set. In the broad safety set, three patients discontinued iptacopan treatment due to TEAEs during the ongoing open-label extension study. All three cases were due to SAEs not related to iptacopan treatment, as determined by the investigator.”¹

The company also reported that “In the controlled safety set, TEAEs leading to study treatment interruption were reported in 10.5% and 11.1% of patients in the iptacopan and placebo groups, respectively. The most frequently reported TEAE leading to interruption of iptacopan treatment was COVID-19 (reported in four patients, 10.5%). In the broad safety set, TEAEs leading to study treatment interruption were reported in 10.9% of patients. In addition, one patient had a temporary dose reduction due to non-serious tonsillar hypertrophy.”¹

EAG comment: The company was asked to clarify the nature of these SAEs and the rationale for concluding that they were unrelated to iptacopan, as the CS stated that three patients discontinued iptacopan due to AEs (all in the open-label extension study), with SAEs determined not to be related to iptacopan. The company provided the details regarding the three patients who discontinued iptacopan due to SAEs in the open-label extension study,

- “One patient discontinued iptacopan due to an SAE of renal impairment

- One patient discontinued iptacopan due to an SAE of C3G (post-transplant recurrent patient with C3G progression confirmed in kidney biopsy)
- One patient discontinued iptacopan due to an SAE of acute kidney injury from immune complex glomerulonephritis (post-transplant recurrent patient with several confounding events leading to eGFR decline, none of which were suspected to be related to iptacopan by the investigator; the investigator suspected postinfectious, crescentic glomerulonephritis on top of not yet remitted C3G as the cause of the acute kidney injury)”⁴

3.2.7.6 Adverse events of special interest

The company reported that “The AEs of special interest for iptacopan were determined based on its mechanism of action, pre-clinical safety studies and clinical studies, and include infections caused by encapsulated bacteria, testicular effects, thyroid changes, malignancy, hypersensitivity, and decreased platelets.”¹

The company further reported that “In the controlled safety set, three patients in the iptacopan group and one patient in the placebo group were reported to have infections caused by encapsulated bacteria. Additionally, one patient in the placebo group experienced a non-serious TEAE of blood thyroid stimulating hormone increased. In the broad safety set, 10 patients (including the three described above in the controlled safety set) were reported to have infections caused by encapsulated bacteria. Most patients had infections that were non-serious and not considered to be related to iptacopan treatment. All infections resolved and patients either continued iptacopan treatment or resumed after resolution of the infection. Additionally, eight patients reported AEs recorded as hypersensitivity, but these were not considered related to iptacopan treatment. No AEs of special interest related to testicular effect, malignancy or decreased platelet count were reported in either safety population.”¹ Further details can be found in Table 3.34.

Table 3.34: Summary of AEs of special interest

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients with at least one event, n (%)			
Infections caused by encapsulated bacteria	3 (7.9)	1 (2.8)	10 (9.9) ^c
As per pre-defined search criteria			
Otitis media	2 (5.3)	0	5 (5.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Cellulitis	0	0	1 (1.0)
Otitis media acute	0	0	1 (1.0)
Pneumococcal sepsis	0	0	1 (1.0)
Streptococcal bacteraemia ^a	0	0	1 (1.0)
Urethritis gonococcal	0	1 (2.8)	0
Manual search^b			
Blood culture positive	1 (2.6)	0	1 (1.0)
Septic shock	0	0	1 (1.0)
Intervertebral discitis	0	0	1 (1.0)

	Controlled safety set		Broad safety set
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Serious or severe infections	2 (5.3)	0	9 (8.9)
Blood culture positive	1 (2.6)	0	1 (1.0)
Infected bite	1 (2.6)	0	1 (1.0)
Pneumonia pneumococcal	0	0	2 (2.0)
Appendicitis	0	0	1 (1.0)
Gastroenteritis	0	0	1 (1.0)
Intervertebral discitis	0	0	1 (1.0)
Norovirus infection	0	0	1 (1.0)
Pelvic inflammatory disease	0	0	1 (1.0)
Pneumococcal sepsis	0	0	1 (1.0)
Pneumocystis jirovecii pneumonia	0	0	1 (1.0)
Pneumonia	0	0	1 (1.0)
pyelonephritis	0	0	1 (1.0)
Septic shock	0	0	1 (1.0)
Streptococcal bacteraemia ^a	0	0	1 (1.0)
Hypersensitivity	0	0	8 (7.9)
Rash	0	0	5 (5.0)
Eczema	0	0	1 (1.0)
Hand dermatitis	0	0	1 (1.0)
Periorbital dermatitis	0	0	1 (1.0)
Rhinitis allergic	0	0	1 (1.0)
Thyroid changes	0	1 (2.8)	0
Blood thyroid stimulating hormone increased	0	1 (2.8)	0
Based on Table 30 of the CS¹ ^a AE was reported verbatim as septic shock (due to streptococcal bacteraemia). ^b Manual search included serious/severe infection in SOC Infections and infestations and HLGTT Microbiology and serology investigations. ^c The total number of patients within the broad safety set with at least one event (n=10) includes otitis media (five patients), otitis media acute (one patient), pneumonia pneumococcal/pneumococcal sepsis/streptococcal bacteraemia (evolved to septic shock)/blood culture positive (all in one patient), pneumonia pneumococcal/septic shock (both in one patient), cellulitis (one patient), and intervertebral discitis (one patient). AE = adverse event; CS = company submission; HLGTT = High Level Group Terms; n = number of patients with at least one event; SOC = System Organ Classes			

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In terms of the indirect and mixed treatment comparisons, the company made the following statement:

- “The APPEAR-C3G trial and the historical eGFR analyses presented in previous Sections are considered to provide a robust source of standard of care (SoC) data in C3G. Background

medications received by the patient population in APPEAR-C3G were considered reflective of UK clinical practice by clinicians. Therefore, data from APPEAR-C3G (including historical data) were deemed suitable to inform the comparison of iptacopan with established clinical management (SoC comparator) in the economic model.

- *Comparative data versus eculizumab were not available from the iptacopan three clinical trial programme in C3G. Whilst eculizumab is considered of limited relevance as a comparator for this submission, the feasibility of an ITC was assessed for completeness. The clinical trials SLR (Appendix B) identified three trials which assessed eculizumab for C3G. However, none of the three studies reported eGFR results, the outcome of interest for the economic model. In addition, sample sizes were small, ranging from 4–6 patients across each of the three trials. None of the studies were conducted in the UK, and thus did not reflect the patient population who is eligible to receive eculizumab under the NHS England commissioning policy criteria. Overall, an ITC was not considered feasible.”¹*

Given that the company stated that ITC analysis for the comparison of iptacopan versus eculizumab was not feasible because the outcome (eGFR) used in the economic model was not reported in the eculizumab trials, the EAG asked the company to conduct ITC analyses based on other outcomes (e.g. proteinuria) that were reported in the eculizumab trials for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence, by using the post-transplant recurrent cohort of the Phase 2 trial of iptacopan.

In responding to the EAG request, the company made the following statement:⁴

- *“ITC versus eculizumab was not deemed feasible for a number of reasons, as noted in Section 2.9 of the CS with further details provided in Section B.1.7 of Appendix B. These reasons included the small sample sizes of the identified eculizumab trials (4–6 patients each) as well as the limited generalisability of the eculizumab trial populations to how eculizumab is used in UK clinical practice.*
- *The clinical trials SLR identified three trials which assessed eculizumab for C3G. Two single-arm, single-centre trials from the US and Turkey included 6 C3G patients treated with eculizumab each, while the third single-arm trial from Italy included overall 10 patients, 4 of which had C3G and were treated with eculizumab.*
- *None of the studies reported inclusion criteria that were similar to the NHS England Clinical Commissioning Policy, which restricts use of eculizumab in the UK to a subset of patients with post-transplant recurrence of C3G and meeting very specific criteria indicative of highly aggressive disease; this includes evidence of active glomerulonephritis with cellular crescents on kidney biopsy and a >20% decline in eGFR within the previous three months. Therefore, findings from the three international studies identified in the SLR may not be generalisable to eculizumab use in UK clinical practice.*
- *With regards to outcomes, none of the three studies reported eGFR data (the outcome of interest for economic modelling) for patients with C3G treated with eculizumab. An ITC of proteinuria outcomes was not considered meaningful due to marked differences in the eculizumab trial populations and the patients included in the post-transplant recurrent cohort of the iptacopan Phase 2 trial. The three eculizumab trials enrolled patients with proteinuria >3.5 g/day, ≥3 g/day, and >1 g/day, respectively (see Appendix B, Table 11). In contrast, elevated proteinuria was not an inclusion criterion for the post-transplant cohort in the iptacopan Phase 2 trial; accordingly, the enrolled patients’ proteinuria levels were predominantly normal at baseline, with a geo-mean*

of 0.28 g/day. Therefore, an ITC of proteinuria reduction outcomes was considered not to provide meaningful results.

- *An ITC of iptacopan versus eculizumab was overall not considered feasible, however, as outlined in the response to clarification question A3, given the very limited role of eculizumab in UK clinical practice, Novartis considers this a minor limitation of this submission. ”*

EAG comment:

- The company stated in the evidence submission that ITC analysis for the comparison of iptacopan versus eculizumab was not feasible because the outcome (eGFR) used in the economic model was not reported in the eculizumab trials. Therefore, the EAG asked the company to conduct ITC analyses based on other outcomes (e.g. proteinuria) that were reported in the eculizumab trials for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence, with the use of the post-transplant recurrent cohort of the Phase 2 trial of iptacopan.
- In responding to the EAG’s request, the company stated that an ITC of proteinuria outcomes was not considered meaningful due to marked differences in the eculizumab trial populations and the patients included in the post-transplant recurrent cohort of the iptacopan Phase 2 trial. The three eculizumab trials enrolled patients with proteinuria >3.5 g/day, proteinuria ≥ 3 g/day, and proteinuria >1 g/day, respectively. However, elevated proteinuria was not an inclusion criterion for the post-transplant cohort in the iptacopan Phase 2 trial; the enrolled patients’ proteinuria levels were predominantly normal at baseline, with a geo-mean of 0.28 g/day.
- The EAG agreed that given the substantial differences of proteinuria levels at baseline between the included patients from the three eculizumab trials and the patients included in the post-transplant recurrent cohort of the iptacopan Phase 2 trial, it would be less meaningful to conduct an ITC based on proteinuria outcomes from these trials.
- Given that an ITC analysis for the comparison of iptacopan versus eculizumab was not conducted, the EAG considered that there was a lack of evidence on the relative efficacy between iptacopan and eculizumab for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence, which implies a key issue.

3.4 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.5 Conclusions of the clinical effectiveness Section

The CS, Appendix B and response to clarification^{1,4,6} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on the clinical efficacy and safety of iptacopan and any potentially relevant comparators in the treatment of C3G. Searches were conducted in October-December 2021 and updated in October 2024. Searches were transparent and reproducible, and a good range of bibliographic databases, conference proceedings, trials registers and grey literature resources were searched. Overall, the EAG has no concerns about the literature searches conducted.

The study selection criteria for participants, interventions, comparators and outcomes in the SLR of clinical effectiveness generally encompassed those specified by the NICE final scope. The data extraction process was satisfactory and in line with recommended good practice in SLRs. The process for the assessment of risk of bias in the included studies was satisfactory. The process of assessing risk of bias and the number of reviewers involved were described. The number of studies retrieved, screened

and included was clear based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart.

One pivotal RCT was identified as being relevant to the SLR: one RCT (APPEAR-C3G) provided the main source of evidence. APPEAR-C3G (NCT04817618) is an international, multicentre, randomised, double-blind, parallel group, placebo-controlled Phase 3 study to evaluate the efficacy and safety of iptacopan in patients with native kidney C3G. Phase 2 study [NCT03832114] and an open label extension study were identified that provided supportive evidence of the clinical efficacy of iptacopan for the treatment of patients with C3G. The Phase 2 study (NCT03832114) was an international, multicentre, open-label, single-arm, non-randomised study in adults with biopsy-confirmed C3G. The open label extension study provided data on the long-term clinical efficacy and safety of iptacopan for the treatment of patients with C3G.

The results of APPEAR-C3G trial showed that, at 6-month follow-up (double-blind period), iptacopan treatment was associated with a statistically significant reduction in 24-hour UPCR by 35.1% (95% confidence interval [CI]: 13.8%, 51.1%) following 6 months of treatment compared with placebo (both arms as add-on to background therapy). The results from the open-label period of APPEAR-C3G showed that among patients initially randomised to iptacopan, the observed reduction in 24-hour UPCR was sustained up to Month 12 (40% geometric mean reduction from baseline; geometric mean ratio 0.60 (95% CI: 0.45, 0.80). At 6-month follow-up (double-blind period), the adjusted mean difference (MD) of eGFR for iptacopan treatment versus placebo was 2.16 ml/min/1.73 m² (95% CI: -2.75, 7.06). The results from the open-label period of APPEAR-C3G showed that at 12-month follow-up, the mean changes from baseline in eGFR in the iptacopan arm and the placebo-iptacopan switch arm were 0.44 ml/min/1.73 m² (95% CI: -3.76, 4.64) and 1.15 ml/min/1.73 m² (95% CI: -3.22, 5.53), respectively.

In terms of the ITC analysis, the company stated in the evidence submission that ITC analysis for the comparison of iptacopan versus eculizumab was not feasible because the outcome (eGFR) used in the economic model was not reported in the eculizumab trials. Therefore, the EAG asked the company to conduct ITC analyses based on other outcomes (e.g. proteinuria) that were reported in the eculizumab trials for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence, with the use of the post-transplant recurrent cohort of the Phase 2 trial of iptacopan.

In responding to the EAG's request, the company stated that an ITC of proteinuria outcomes was not considered meaningful due to marked differences in the eculizumab trial populations and the patients included in the post-transplant recurrent cohort of the iptacopan Phase 2 trial. The three eculizumab trials enrolled patients with proteinuria >3.5 g/day, proteinuria ≥3 g/day, and proteinuria >1 g/day, respectively. However, elevated proteinuria was not an inclusion criterion for the post-transplant cohort in the iptacopan Phase 2 trial; the enrolled patients' proteinuria levels were predominantly normal at baseline, with a geo-mean of 0.28 g/day.

The EAG agreed that given the substantial differences of proteinuria levels at baseline between the included patients from the included eculizumab trials and the patients included in the post-transplant recurrent cohort of the iptacopan Phase 2 trial, it would be less meaningful to conduct an ITC based on proteinuria outcomes from these trials.

Given that an ITC analysis for the comparison of iptacopan versus eculizumab was not conducted for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive

C3G recurrence, the EAG considered that there was a lack of evidence on the relative efficacy between iptacopan and eculizumab for the subgroup of patients who have previously had a kidney transplant and who have highly aggressive C3G recurrence, which implies a key issue.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of CEA studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 *Searches performed for cost effectiveness Section*

The following paragraphs contain summaries and critiques of all searches related to economic evidence, health-related quality of life (HRQoL) and resource use identification presented in the CS.¹ Canada's Drug Agency (formerly the CADTH) evidence-based checklist for the PRESS was used to inform this critique.⁵ The EAG has presented only the major limitations of each search strategy in the report.

Appendices E F and G of the CS provide details of SLRs conducted to identify relevant studies on cost effectiveness, cost/health care resource use and HRQoL in the treatment of C3G.^{13, 14}

EAG comment:

- Separate searches were undertaken to identify relevant studies on the economic evidence and health care cost/resource use in the treatment of C3G and HRQoL data. The CS, Appendices E F and G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 4, 13, 14}
- The following databases were searched for the economic evidence, healthcare resource use and HRQoL SLRs: Embase, MEDLINE, CDSR and CENTRAL. The searches for economic evidence were conducted on 16 September 2020 and updated on 10 October 2024. The searches for healthcare resource use were conducted on 11 February 2021 and updated on 10 October 2024. HRQoL searches were conducted on 22 January 2021 and updated on 12 November 2024.
- For the economic SLR conference searches were conducted on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) presentation database and the Health Technology Assessment International (HTAi) website. The healthcare resource use SLR additionally also searched ERA-EDTA and ASN conferences. For the HRQoL searches, ISPOR, the ERA-EDTA and ASN conferences were searched. All conference proceedings searches were limited to 2019-2024.
- A wide range of websites were searched for all economic/HRQoL searches, including regulatory and HTA bodies' websites, the CEA Registry, the University of Sheffield Health Utilities Database and the EQ-5D Publications Database. Bibliographies of systematic reviews and meta-analyses and other selected studies were reference checked. Supplementary searches were conducted on Google and Google Scholar. Searches were conducted in October 2024 for the economic/healthcare resource use SLR and in November 2024 for the HRQoL SLR.
- No date or language limits were applied to the searches.
- The searches contained a population facet for C3 glomerulopathy. This was then combined with a study design filter containing terms for costs and economic evaluations. The HRQoL searches contained the same population facet for C3 glomerulopathy. This was then combined with a study design filter containing terms for HRQoL.
- All searches were transparent and reproducible, and contained a good range of search terms, synonyms and subject headings.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.1.

Table 4.1: Eligibility criteria for the SLRs

	Inclusion criteria	Exclusion criteria
Patient population	Patients diagnosed with C3G	Any other patient population
Intervention	Any intervention/no intervention for C3G patients; placebo, SoC	N/A
Comparator	Any other intervention/no intervention for C3G patients; placebo, SoC	N/A
Outcomes(s) 1 (Published economic evaluations)	- Model parameters and aspects of model design - Sources of data (baseline risk, treatment effects) - Results (cost, QALY/effectiveness)	Studies not reporting relevant outcomes of interest
Outcomes(s) 2 (Utility studies)	Utilities and HRQoL	Studies not reporting relevant outcomes of interest
Outcomes(s) 3 (Cost/resource use studies)	- Cost (direct and indirect) - HCRU	Studies not reporting relevant outcomes of interest
Study design 1 (CEA studies)	- Any economic evaluation or analysis presenting costs and consequences such as: - CEA - Cost-utility analysis - Cost-benefit analysis - Cost-minimisation analysis - Cost-consequence studies - Budget impact analysis	Case reports, case-series, opinion papers, letters, commentaries, protocol, news, animal/in vitro studies, randomised clinical trial, non-randomised clinical trial
Study design 2 (Utility studies)	- Any study reporting HRQoL - Studies reporting utilities/mapping algorithms from HRQoL to utilities - Studies reporting caregiver burden	Case reports, case-series, editorials, letters, protocols, opinion papers, commentaries, news, narrative and systematic reviews, non-human studies
Study design 3 (Cost/resource use studies)	- Cost studies/surveys/analyses - Database studies collecting cost data - Burden of illness - Resource surveys	Case reports, case-series, editorials, letters, protocols, opinion papers, commentaries, news, narrative and systematic review, non-human studies

	Inclusion criteria	Exclusion criteria
Based on CS Appendices E, F and G ¹³⁻¹⁵ C3G = complement 3 glomerulopathy; CEA = cost-effectiveness analysis; HCRU = health care resource utilisation; HRQoL = health-related quality of life; N/A = not applicable; QALY = quality-adjusted life year; SLRs = systematic literature reviews; SoC = standard of care		

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationales for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with NICE reference case
Perspective on costs	NHS and PSS	Consistent with NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with NICE reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with NICE reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Consistent with NICE reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Consistent with NICE reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Consistent with NICE reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with NICE reference case

Element of HTA	Reference case	EAG comment on CS
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with NICE reference case
CS = company submission; EAG = External Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom		

4.2.2 Model structure

A de novo health-state transition model was developed using a state-transition (Markov) approach to simulate the progression of CKD through to kidney failure and kidney replacement therapy (KRT). The model comprises nine mutually exclusive health states (HSs) (CS, Figure 27):

1. CKD stage 1 (eGFR ≥ 90 ml/min/1.73 m²)
2. CKD stage 2 (eGFR 60–89 ml/min/1.73 m²)
3. CKD stage 3a (eGFR 45–59 ml/min/1.73 m²)
4. CKD stage 3b (eGFR 30–44 ml/min/1.73 m²)
5. CKD stage 4 (eGFR 15–29 ml/min/1.73 m²)
6. CKD stage 5 (eGFR 8–15 ml/min/1.73 m²)
7. Dialysis (KRT initiated at eGFR ≤ 7.6 ml/min/1.73 m²)
8. Post-transplant (KRT initiated at eGFR ≤ 7.6 ml/min/1.73 m²)
9. Death

Key model assumptions:

- Disease progression assumptions
 - eGFR was assumed to decline at a constant rate, regardless of CKD stage.
 - Transitions to less severe CKD stages were not allowed (i.e., no backward transitions).
 - Death was modelled as an absorbing state and could be reached from any other HS.
- Treatment-related assumptions
 - A constant treatment effect was assumed over time, conditional on patients remaining on treatment.
 - Patients discontinuing iptacopan were assumed to receive SoC alone after which no residual iptacopan treatment effect was assumed
 - Patients on iptacopan were assumed to stop treatment at the point of commencing KRT.
 - Patients on SoC were also assumed to stop treatment at the point of commencing KRT, except for ACEis/ARBs which were continued during KRT.
- Initiation of KRT
 - The threshold for initiating KRT was set at eGFR ≤ 7.6 ml/min/1.73 m² (see CS Section 3.3.2.2). At this point, patients either received a pre-emptive transplant (moving to the 'Post-transplant' state) or initiated chronic dialysis ('Dialysis' state).
 - All patients with C3G were assumed to commence KRT following kidney failure; conservative management was not considered.
- Dialysis and transplant assumptions
 - While in the 'Dialysis' state, patients had a (time independent) probability of receiving a transplant each cycle until age 80 years.

- Patients in the 'Post-transplant' state could experience graft failure each cycle, transitioning back to 'Dialysis' (time independent probability).
- The model allowed for multiple transplant-graft failure cycles over the model time horizon.
- The model accounts for different dialysis modalities (haemodialysis [HD], continuous ambulatory peritoneal dialysis [CAPD] and automated peritoneal dialysis [APD]) in estimating costs and utilities:
 - Modality proportions: the distribution of dialysis types was based on RaDaR registry data in patients with C3G: HD: 85.3%, APD: 11.8%, CAPD: 2.9%.
 - Utility valuation: a weighted average utility for dialysis was calculated using the above modality proportions.
 - Cost valuation: dialysis costs were derived from NHS reference costs. HD was assumed to occur three times per week, and APD and CAPD daily. HD costs were further weighted by setting (hospital, satellite, home) based on HRG-coded activity. A weighted average dialysis cost was then calculated using the modality proportions.

EAG comment: The main concerns of the EAG relate to: a) the use of eGFR-based HSs rather than proteinuria reduction (UPCR); b) the eGFR threshold used to initiate KRT; and c) assumptions surrounding repeated kidney transplants.

- a) The company modelled CKD progression using eGFR-based HSs rather than UPCR, despite UPCR being the primary endpoint of APPEAR-C3G. In clarification response B2, the company concluded (while acknowledging the exploratory nature and small sample size of the analyses) that greater UPCR reductions with iptacopan may translate into greater eGFR benefit, while also lower reductions (<30%) were associated with meaningful improvements in eGFR slope compared to pre-treatment trajectories. The company further justified the eGFR-based model structure by citing precedents in previous NICE Technology Appraisals (TAs) (see CS, Table 31) and confirmation from UK clinicians that CKD stage (based on eGFR) is more relevant for estimating quality of life (QoL) and costs in C3G. They also noted that KRT initiation is based on eGFR, not UPCR, and that UPCR-based HSs would still require tracking eGFR to model KRT initiation. Given these points, the EAG considers the use of an eGFR-based structure reasonable.
- b) The use of an eGFR threshold of 7.6 ml/min/1.73 m² to initiate KRT in the model is considered reasonable and justified (based on clarification response B3), as it reflects a weighted average of typical initiation points for both dialysis (around 5–7 ml/min/1.73 m², per NICE guideline NG107) and pre-emptive transplantation (typically at higher eGFR, ~10 ml/min/1.73 m², based on UK registry data and clinical input). While NG107¹⁶ specifically addresses dialysis initiation, the model applies a unified threshold across all KRT modalities. Scenario and sensitivity analyses varying the threshold showed limited impact on cost effectiveness outcomes, indicating that the eGFR threshold to initiate KRT was not a key model driver.
- c) The assumption of multiple kidney transplants in the economic model is consistent with clinical practice for C3G, given high post-transplant recurrence rates (55–85%) and a median graft survival of 6.5 years, as observed in RaDaR data. While the average of 1.9 lifetime transplants in the SoC arm is supported by clinical expert opinion, RaDaR data also show that 19% of transplant recipients had already received two or more transplants, despite the relatively young cohort age. For the iptacopan arm, the model predicts a lower average of 1.46 transplants, which, according to the company, experts deemed plausible due to iptacopan's potential to slow disease progression, though they found it difficult to validate the precise number. Experts advised against capping the maximum number of transplants, as this would not reflect clinical reality. Scenario analyses that reduced or

capped transplant frequency led to lower incremental cost-effectiveness ratios (ICERs), suggesting that the base-case may conservatively overestimate the ICER of iptacopan + SoC compared to SoC. The probabilities of graft failure and repeated transplantation were derived from RaDaR data, incorporating cycle-based probabilities and transplant eligibility assumptions.

4.2.3 Population

Consistent with the NICE scope as well as the pivotal randomised trial (APPEAR-C3G; NCT04817618), the population considered in the CS (CS, Table 1) was adults with C3G. Specifically, native kidney C3G patients with continued risk of disease progression on a maximally tolerated licensed dose of an ACEi or ARB. The anticipated indication of iptacopan in C3G is as follows: “*Iptacopan is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated*” (CS Table 2). The key baseline patient characteristics in the economic model are listed in Table 4.3 below.

Table 4.3: Baseline patient characteristics used in the economic model

	APPEAR-C3G (base-case)	Pooled trial data (scenario)	RaDaR (scenario)
Age (years)	27.9	27.6	28.9
Proportion female	36.5%	36.7%	46.1%
Mean eGFR (ml/min/1.73m ²)	92.8	88.4	78.2
Proportion CKD stage 1	58.1%	52.2%	38.4%
Proportion CKD stage 2	23.0%	23.3%	27.3%
Proportion CKD stage 3a	6.8%	7.8%	10.1%
Proportion CKD stage 3b	9.5%	13.3%	14.1%
Proportion CKD stage 4	2.7%	3.3%	10.1%
Based on CS, Table 33 ¹ C3G = complement 3 glomerulopathy; CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; RaDaR = National Register of Rare Kidney Diseases			

EAG comment: The RaDaR registry data indicated that the baseline patient characteristics in the APPEAR-C3G potentially do not accurately reflect UK clinical practice as the proportion of females in APPEAR-C3G is lower and the clinical characteristics (e.g. mean eGFR and CKD stage) do seem to reflect a healthier population in APPEAR-C3G. In response to clarification question A10 (referred to in B1) the company indicated that indeed RaDaR patients were, on average, diagnosed with higher UPCR and a lower eGFR, indicating more advanced disease at time of diagnosis, than patients enrolled in APPEAR-C3G. Moreover, baseline mean UPCR of APPEAR-C3G participants was higher (3.40 g/g) compared to the prevalent RaDaR cohort (1.73 g/g). According to the company this reflects that APPEAR-C3G focused on a population at higher risk of disease progression. Therefore, the EAG preferred to use the baseline patient characteristics as observed in the RaDaR registry in its base-case. Notably this does not affect treatment effectiveness (as this is based on the population as observed in the APPEAR-C3G trial).

4.2.4 Interventions and comparators

The intervention is modelled as iptacopan + SoC, in line with the APPEAR-C3G trial and the proposed positioning of iptacopan in the C3G treatment pathway (CS, Figure 5). Iptacopan is modelled as 200 mg oral capsules which are taken b.i.d.

In line with the final scope of this appraisal, the comparator is SoC alone (see CS, Section 1.3.5) consisting of:

- ACEi (ramipril; 47.3%)
- ARB (losartan; 52.7%)
- CoS (prednisolone; 32.4%)
- MMF (36.5%)
- SGLT2in (dapagliflozin; 5.4%)

Patients can receive multiple SoC treatments simultaneously (aligning with CS, Figure 3). However, regarding ACEi and ARB use, guidelines generally recommend the use of one or the other.

Eculizumab was included in the final scope for people who have previously had a kidney transplant and who have highly aggressive C3G recurrence as specified in the NHS England clinical commissioning policy for eculizumab. However, the company did not include eculizumab as a comparator.

EAG comment: The main concerns of the EAG relate to: a) representativeness of SoC as observed in the APPEAR-C3G trial for UK clinical practice; and b) the exclusion of eculizumab as comparator.

- a) It is unclear to the EAG to what degree the SoC as observed in the APPEAR-C3G trial is consistent with the RaDaR registry data and UK clinical practice. According to the company (response to clarification question A10), their advisors agreed that the concomitant medications (including ACEi/ARBs) in APPEAR-C3G were appropriate and representative of management of C3G patients within UK clinical practice. Nevertheless, the EAG believes a scenario analysis including SoC treatment distribution based on RaDaR would be informative. Notably this only affects the SoC costs (SoC effectiveness is based on SoC as observed in the APPEAR-C3G trial).
- b) Inconsistent with the scope and the NHS England clinical commissioning policy for eculizumab, eculizumab was not included as a comparator in the economic model. In response to clarification question A3 (referred to in B6), the company highlighted three main reasons for not including eculizumab: a) limited evidence (no head-to-head data and an ITC was deemed infeasible by the company); b) limited relevance as a comparator iptacopan; and c) limited use of eculizumab in UK clinical practice for the population of interest (see Section 2 for further details).

4.2.5 Perspective, time horizon and discounting

The analysis was performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was 3 months with a lifetime time horizon (72.1 years, i.e., up to age 100 years) and a half-cycle correction was applied.

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for iptacopan + SoC and SoC alone is the APPEAR-C3G trial.

4.2.6.1 Modelling of disease progression

The company modelled transitions through CKD stages using eGFR slopes (the rate of eGFR decline, defined as the average change in eGFR in a 1-year period). The time to move between CKD stages 1 to 5 was defined as the time taken for eGFR to decline from the midpoint of the current CKD stage to the midpoint of the following stage, assuming a uniform distribution of patients across a CKD stage. Transitions to KRT were modelled to take place at the KRT threshold (7.6 ml/min/1.73 m²) instead of the midpoint value. Although the company acknowledged that the rate of eGFR decline may vary over the course of disease, it assumed that the speed of progression in the economic model was independent of CKD stage and constant over the model time horizon.

The company considered three options for estimating the eGFR slope for both treatment strategies (see Table 4.4):

- 1) Randomised comparison using APPEAR-C3G (CS scenario analysis).
- 2) Iptacopan before-after comparison using APPEAR-C3G including the open-label extension study (CS base-case).
- 3) Iptacopan before-after comparison using APPEAR-C3G and Phase 2 native kidney cohort A including the open-label extension study (CS scenario analysis).

The company selected the iptacopan before-after comparison using APPEAR-C3G including the open-label extension study (option 2) for their base-case whereas the other two options were explored in scenarios. The selected eGFR slopes were used to calculate the 3-month per cycle probability of disease progression (see Table 4.4).

Table 4.4: Rates of eGFR decline and per cycle probabilities of progression to next state

Option	Analysis	Rate of eGFR decline ml/min/1.73 m2/year (95% CI)	Probability of progression to next state (per 3-month cycle)					
			CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	CKD 5
Randomised comparison using APPEAR-C3G (CS scenario)								
SoC	Placebo arm data from 6-month double-blind period (N=36)	-3.079 (-10.131, 3.973)	1.8%	3.4%	5.0%	5.0%	6.6%	18.7%
Iptacopan	Iptacopan arm data from 6-month double-blind period (N=38)	-0.025 (-6.929, 6.878)	0.01%	0.03%	0.04%	0.04%	0.06%	0.17%
Treatment effect	3.053 ml/min/1.73 m²/year, 95% CI (−6.815, 12.922)							
Iptacopan before-after comparison using APPEAR-C3G including the open-label extension study (CS base-case)								
SoC	Pre-iptacopan data, up to 2.5 years (N=74)*	-7.224 (-10.101, -4.348)	4.2%	7.7%	11.3%	11.3%	14.9%	38.4%
Iptacopan	On-iptacopan data, up to 2 years	-0.289 (-3.884, 3.305)	0.2%	0.3%	0.5%	0.5%	0.6%	1.9%

Option	Analysis	Rate of eGFR decline ml/min/1.73 m2/year (95% CI)	Probability of progression to next state (per 3-month cycle)					
			CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	CKD 5
	treatment duration (N=74)**							
Treatment effect	6.935 ml/min/1.73 m ² /year, 95% CI (3.481, 10.390)							
<i>Iptacopan before-after comparison using APPEAR-C3G and phase 2 native kidney cohort A including the open-label extension study (CS scenario)</i>								
SoC	Pre-iptacopan data, up to 2.5 years (N=90)*	-8.317 (-10.891, -5.744)	4.8%	8.8%	12.9 %	12.9 %	16.9 %	42.8 %
Iptacopan	On-iptacopan data, up to 4.7 years treatment duration (N=90)**	-0.701 (-3.765, 2.363)	0.42 %	0.78 %	1.16 %	1.16 %	1.55 %	4.60 %
Treatment effect	7.616 ml/min/1.73 m2/year, 95% CI (4.616, 10.616)							
Based on Tables 34 and 35 of the CS ¹								
* Pre-iptacopan data includes historical values (up to 2 years prior to trial enrolment or since C3G diagnosis if less than 2 years), screening/run-in data and placebo arm data from the 6-month double-blind period of APPEAR-C3G.								
** On-iptacopan data includes all data from initiation of iptacopan treatment, including data from patients originally randomised to the placebo arm of APPEAR-C3G after switching to open-label iptacopan at Day 180.								
C3G = complement 3 glomerulopathy; CI = confidence interval; CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; SoC = standard of care								

4.2.6.2 Modelling of KRT

Once patients reached an eGFR value of 7.6 ml/min/1.73 m² in the company's base-case, they were assumed to start KRT (dialysis or a transplant). Out of these, 18.4% were modelled to receive a pre-emptive transplant (based on RaDaR data), while the remaining 81.6% of patients started dialysis. For patients in the dialysis HS, a per-cycle probability of 8.7% receiving a transplant was modelled (based on RaDaR data). Based on Adelphi Disease Specific Programme (DSP) survey data, 16.8% of patients in need of a transplant were assumed ineligible and remained in the dialysis HS until death. Additionally, patients aged ≥80 years were assumed not to receive a transplant. For patients that received a transplant, a 2.6% probability of graft failure was modelled per cycle, after which patients returned to the dialysis HS. The company modelled repeated transplantation following graft failure, however, it was assumed that a proportion of patients was no longer eligible for another transplant (16.8%, i.e., the same as ineligibility for first transplant). All input values related to KRT are summarised in the CS, Table 36.

4.2.6.3 Modelling of treatment discontinuation

The discontinuation rate among patients on iptacopan before reaching kidney failure was based on all-cause treatment discontinuation of iptacopan in the pooled APPEAR-C3G, Phase 2 and extension studies (broad safety set), resulting in a per cycle (3 months) discontinuation probability of 1.57%. SoC treatments were assumed not to be discontinued prior to kidney failure. For both iptacopan and SoC it was assumed that patients would discontinue treatment at the point of commencing KRT, except for

ACEi/ARB as these would usually be continued according to UK clinicians. Patients who discontinued iptacopan, either before or upon reaching kidney failure, were assumed to subsequently receive SoC alone with the SoC eGFR slope applied from the point of discontinuation onwards.

4.2.6.4 *Modelling of mortality*

The company informed mortality in its economic model using mortality ratios, standardised to the general population of England and Wales for patients in RaDaR with and without kidney failure, from a study by Wong 2024¹⁷ (CS, Table 39). In this study, a total of 27,285 people from the UK with rare kidney diseases were analysed, including 1,089 people with either C3G or MPGN.

EAG comment: The main concerns of the EAG relate to: a) the data used for generating eGFR slopes, b) the assumption that the speed of progression in the economic model was independent of CKD stage and constant over the model time horizon, c) the modelling of treatment discontinuation, d) the assumption of a constant iptacopan treatment effect over the model time horizon while patients remained on treatment, and e) the approach for modelling disease progression.

- a) The company estimated eGFR slopes using a before-after comparison (i.e., pre-iptacopan data for SoC and on-iptacopan data for iptacopan) based on APPEAR-C3G including the open-label extension study. This approach is considered suboptimal by the EAG as the resulting iptacopan treatment effect was based on an observational comparison rather than a randomised comparison (based on APPEAR-C3G trial, i.e., CS, option 1) and is therefore prone to bias. The company, however, considered the SoC eGFR slope based on the randomised double-blind period of APPEAR-C3G to be implausible based on clinical advisors input and inconsistency with published literature, their clinical experience and real-world RaDaR data on the median time from diagnosis to kidney failure. Therefore, the EAG requested additional scenario analyses in clarification question B7 using 1) RaDaR data (all C3G patients, n=139) and 2) pre-iptacopan data (i.e., CS option 2) to inform the eGFR slope of SoC, and subsequently apply the iptacopan treatment effect as observed in the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope. Both scenario analyses resulted in substantially increased ICERs. All alternatives considered, the EAG regards the approach of estimating the eGFR slope for SoC based on RaDaR and subsequently applying the iptacopan treatment effect from the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope to be the most reasonable for (relative) treatment effectiveness in the economic model and adopted this in its EAG base-case. This approach preserves randomisation for the estimated treatment effect and uses the SoC eGFR slope based on real-world RaDaR data. Additionally, an EAG scenario analysis was explored informing the eGFR slope in both arms based on the randomised double-blind period of APPEAR-C3G.
- b) The EAG questions the company's assumption that the speed of progression in the economic model was independent of CKD stage and constant over the modelled time horizon. In response to clarification question B7e, the company stated based on clinical expert inputs that a linear slope was a reasonable simplification as the overall path of disease in C3G is a progressive decline. In addition, it was stated that unlike other kidney diseases, in C3G eGFR decline does not tend to get steeper as patients get closer to kidney failure. The company provided CKD-specific eGFR slopes which the EAG did not consider informative, as these were limited to the patient's CKD stage at baseline rather than providing the rate of decline while moving through CKD stages. Additionally, time-dependent eGFR decline rates were provided in Table 5 of the clarification response, indicating that eGFR slopes varied over time over the pre-randomisation, double-blind and open-label treatment periods. The EAG therefore considers the company's assumption of a constant, CKD-independent decline rate over time to be potentially implausible and insufficiently justified.

Over- or underestimation of the speed at which patients progress in the economic model is likely to have significant implications for the long-term modelling of costs and effects, particularly those associated with KRT such as dialysis and kidney transplantation. The EAG therefore considers this to be a key issue.

- c) The company modelled a constant treatment discontinuation rate of 0.063 per year for patients on iptacopan who have not reached kidney failure based on all-cause treatment discontinuation of iptacopan in the pooled APPEAR-C3G, Phase 2 and extension studies (broad safety set). The EAG questioned the plausibility of assuming a constant discontinuation rate over time and therefore requested additional analyses including time-varying discontinuation rates. The company provided time to treatment discontinuation (TTD) analyses for both the pooled data and for the APPEAR-C3G trial only. Scenario analyses were presented for the exponential and log-normal curves as these had the best statistical fit (AIC/BIC), which had a minor impact on the cost effectiveness results. However, the impact of these TTD analyses may be more pronounced when waning of the iptacopan treatment effect is additionally incorporated in the economic model (comment d) below). It was further stated that clinical experts agreed on the exponential curve resulting in the most plausible extrapolation of TTD, whereas the Weibull and Gompertz extrapolations were considered implausible. The EAG noted, however, that the company did not provide further details on these clinical expert inputs, and that various other criteria from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance to assess the most suitable parametric model were lacking (e.g. evidence to assess the clinical plausibility of the long-term TTD estimates resulting from the parametric survival curves). Considering the currently available evidence, the EAG considers the statistical fit of all curves to be within an acceptable range except for the generalised gamma (specifically the Bayesian information criterion [BIC]). However, the company should provide full details of the TTD model selection process based on the NICE DSU TSD 14 guidance for the EAG to assess the most appropriate curve to inform treatment discontinuation in the economic model.
- d) The company assumed a constant iptacopan treatment effect over the model time horizon while patients remained on treatment. The EAG considers that this strong assumption required further exploration. Consequently, the EAG requested further justification and evidence that supports the company's assumption, as well as scenario analyses exploring waning of the iptacopan treatment effect at different time points. The company argued that the disease-modifying effect of iptacopan was sustained throughout the APPEAR-C3G trial and that clinical experts agreed that the treatment effect is not expected to wane. Also, the EAG's clinical expert agreed that *"the on-target effect on complement inhibition will remain comparable throughout"*. However, the company did not provide the evidence requested by the EAG in clarification question B9b to assess potential treatment waning, stating that this was not deemed feasible due to the limited number of CKD stage transitions were observed during APPEAR-C3G. Although acknowledging the clinical expert inputs, the EAG considers the assumption of a constant iptacopan treatment effect over the model time horizon while patients remained on treatment to be insufficiently assessed. Therefore, the EAG would like to see further evidence of a constant treatment effect during the observed period, as requested in clarification question B9b, as well as scenario analyses exploring treatment waning beyond the observed period.
- e) Contrary to several previous TAs where transition probabilities from observed transitions between CKD stages were used to model disease progression, the company used eGFR slopes to transition through CKD stages in the current appraisal. This was justified by the small sample size and the low number of patients in more advanced CKD stages at baseline. Nevertheless, upon request the company explored generating transition probabilities from observed transitions between CKD stages in response to clarification question B7g. Based on the provided results of this analysis, the

EAG agrees that the company's approach of using eGFR slopes is more appropriate to model disease progression in the economic model.

4.2.7 *Adverse events*

The company's economic model captured SAEs suspected to be related to iptacopan. These were sourced from the broad safety set (pooled trial populations), resulting in four patients experiencing a total of nine SAEs. The company stated that some SAEs were linked and thus merged to a total of five SAEs occurring in 189.9 patient years, giving a SAEs per-cycle probability of 0.66%. The 32.1-day duration of SAEs presentation assumed in the economic model was also sourced from the broad safety set.

The CS detailed that almost all SAEs suspected to be related to iptacopan were infections with encapsulated bacteria (an AE of special interest for iptacopan) leading to pneumonia or consequences thereof such as sepsis and thus proceeded to standardise them to pneumonia and sepsis in the economic analysis in a simplifying assumption. **EAG comment:** The main concerns of the EAG relate to: a) the definition of AEs relevant for the CS DP, b) evidence used to identify AEs, c) standardisation and merging of SAEs.

- a) The EAG considers the company's definition of AEs relevant to the DP, i.e., SAEs suspected to be related to iptacopan, to be unsatisfactory. First, it diverges from Common Terminology Criteria for Adverse Events (CTCAE) for AEs. Second, it is unclear how "suspected to be related to iptacopan" was assessed and clinically justified. The definition impeded an inclusion of AEs for the comparators, thereby preventing an assessment of differences in consequences on health outcomes and resource use as stipulated by NICE. Upon inquiry, the company explained while CS and MF are associated with side effects, ACEis and ARBs were considered well tolerable by clinical experts.⁴ The EAG is concerned that safety profiles might differ when the comparator treatments are given respectively when iptacopan is added, to which the company highlighted that the iptacopan AEs reflect a patient population where it is added to background SoC. Nevertheless, the EAG supports the company's claim having chosen a conservative approach by disregarding consequences of comparator AEs. The company stressed that the definition of SAEs was also used in an earlier NICE appraisal of iptacopan.¹⁸ The EAG considered the CTCAE definition to be the most appropriate and modelled all severity grade 3+ AEs (incidence >0%) irrespective of a suspected relationship with iptacopan in its base-case.
- b) Whereas the modelled CS population was native kidney C3G patients with continued risk of disease progression on a maximally tolerated licensed dose of an ACEi or ARB, i.e., in line with the inclusion criteria of APPEAR-C3G (see EAG report Section 4.2.3), the company used the broad safety set (including patients with post-transplant recurrence) to inform SAEs in its base-case. The decision for the broad safety set was supported by two clinical experts consulted by the company¹⁹ upon EAG clarification question B10b as it increases exposure duration (patient-years) substantially. The EAG's clinical expert agreed with the company's reasoning.¹⁹ In the iptacopan arm of the controlled safety set (APPEAR-C3G trial), three SAEs and one of them related to iptacopan were identified during 18.3 patient years.²⁰ (Table 2.1). Although the EAG acknowledges the substantially increased exposure duration with the broad safety set, it is unclear what the impact of differences between the CS population and the broad safety population may be on modelling of AEs. Thus, the EAG decided to rely on the controlled safety set in its EAG base-case analysis.
- c) The company's standardisation of all SAEs to pneumonia/sepsis further constraints the health economic assessment, taking into account the few AEs the company considered relevant for the submission. However, as the clinical expert consulted by the EAG agrees with the company's

rationale based on the chosen definition of relevant AEs,¹⁹ the EAG considers the company's approach to be reasonable. Next to that, the company merged SAEs in its base-case which it assumed to be linked, stating that these occurred concurrently and concerned pneumonia progressing to sepsis. However, this may underestimate resource use and impact on HRQoL of these events. Whereas it is reassuring that the EAG clinical expert agrees with the company's rationale,¹⁹ the EAG is concerned that the impact on AE-related costs and health benefits remains unknown.

4.2.8 HRQoL

The utility values considered in the CS were based on the APPEAR-C3G clinical trial and literature.

4.2.8.1 HRQoL data identified in the literature review

A SLR, updated most currently in November 2024, identified two studies in C3G which provided utility values, but these were considered insufficient. The first study, a randomised clinical trial, reported European Quality of Life-5 Dimensions 5-Level (EQ-5D-5L)-based utility values at baseline and 26 weeks yet not HS-specific ones.²¹ The second study reported utility values for CKD stages 1 to 4/5 derived from the EQ-5D-5L, mapped with the United States (US) tariff.²² It was discarded in the CS because CKD stage 1 patients had the worst HRQoL after patients with CKD stage 4/5.

Additionally, NICE TAs on general CKD published in the last 10 years were reviewed and 13 TAs identified.¹ (Table 42). The studies by Jesky 2016²³ and Lee 2005²⁴ were the main sources that informed utilities for CKD stages 1 to 5 and dialysis and transplant, respectively.

4.2.8.2 Health state utility values

EQ-5D-5L data was sourced from the APPEAR-C3G trial for CKD stages 1 to 4 and mapped to EQ-5D-3L with the Hernandez-Alava 2022²⁵ algorithm in line with NICE recommendations. A mixed effects linear regression model for repeated measures provided utility values for the economic model. The model included the covariates CKD stage, age, sex, and baseline utility. The company pooled CKD stage 1 and 2 utilities in its base-case since it perceived the lower stage 1 value to be implausible. CKD stage 5 utility was informed by Jesky 2016,²³ providing European Quality of Life-5 Dimensions 3-Levels (EQ-5D-3L) data from a CKD (any aetiology) UK study population of 64 years in median age. Dialysis and post-transplant utilities by Lee 2005,²⁴ providing EQ-5D-3L data from a UK kidney failure population (N=416) of 58.2 years and 55.5 years in mean age, for males and females respectively. A joint dialysis utility value was derived as a weighted average of 85.3% of C3G patients getting HD and 14.7% getting peritoneal dialysis (PD), based on the RaDaR study.²⁶ The HS utilities from these different study populations were adjusted for the age- and sex-matched general population utility from Hernandez-Alava,²⁵ employing a utility multiplier. Likewise, the age-related decline in health over time was captured. In a scenario, all CKD HS utilities were informed by Jesky 2016²³ instead of APPEAR-C3G. A summary of utility values used in the company's base-case is provided in Table 4.5.

Table 4.5: Health state utility values

Health state	Reported utility value for study population (95% CI)	Reference	Modelled utility at baseline (adjusted for age and sex)	Justification
CKD stage 1	0.91		0.91	

Health state		Reported utility value for study population (95% CI)	Reference	Modelled utility at baseline (adjusted for age and sex)	Justification
CKD stage 2		0.91	APPEAR-C3G ²⁷	0.91	UK clinical and health economic expert opinion
CKD stage 3a		0.86		0.86	
CKD stage 3b		0.86		0.86	
CKD stage 4		0.85		0.85	
CKD stage 5 (pre-KRT)		0.73 (0.62–1.00)	Jesky 2016 ²³	0.81	UK clinical and health economic expert opinion
Dialysis	HD	0.44 (SD: 0.32)	Lee 2005 ²⁴	0.49	UK clinical and health economic expert opinion
	PD	0.53 (SD: 0.34)		0.58	
Post-transplant		0.71 (SD: 0.27)			
Based on Table 43 of the CS ¹ C3G = complement 3 glomerulopathy; CI = confidence interval; CKD = chronic kidney disease; CS = company submission; KRT = kidney replacement therapy; HD = haemodialysis; PD = peritoneal dialysis; SD = standard deviation; UK = United Kingdom					

4.2.8.3 Disutility values

Based on the CS reasoning detailed in Section 4.2.7, standardising all SAEs to pneumonia and sepsis, the company included a single disutility for infections for iptacopan in the economic model. It was taken from Oppong 2013,²⁸ who reported a 0.156 utility difference from acute presentation of cough and lower respiratory tract infections to recovery at week 4 in English patients based on EQ-5D-3L.

EAG comment: The main concerns of the EAG relate to: a) (face) validity of the chosen CKD stage 5+ utilities b) the longitudinal data regression analyses of APPEAR-C3G trial data to inform CKD stages 1-4 in the health economic model, c) issues related to early CKD stages, and d) validity of chosen disutility value

- a) For CKD stage 5+, the company informed utility values in their economic model by literature. As these studies reported from divergent and substantially older patient populations, the company adjusted for age and gender to match the modelled patient population (baseline mean age: 27.9 years). However, the EAG is apprehensive of the steep decline from CKD stage 4 to 5+, with the 5+ CKD stage utilities potentially capturing general CKD comorbidities apparent in later ages yet not applicable for C3G specifically. The clinical advisor consulted by the company deemed the post-transplant HS utility (0.76) “relatively low” and supported alternatively the use of Liem 2008² value (0.81)^{29, 30} In the health economic model, patients treated with the comparator treatments spend more time in the dialysis and post-transplant HSs, implying significant consequences of the choice of higher CKD stage utility values for the CEA. In response to clarification question B13, the company stressed the considerable impact of KRT on HRQoL, the use of Lee 2005²⁴ utility values in prior TAs⁴ (Table 34) and shortcomings related to the Liem 2008²⁹ meta-analysis. However, the Liem 2008²⁹ was also considered appropriate in prior TAs⁴ (Table 34) and increased the ICER by [REDACTED] in a provided scenario analysis by the company when solely the post-

transplant utility was adjusted, highlighting the immense impact on uncertainty surrounding CKD stage 5+ values derived from the wider CKD literature. The EAG clinical expert highlighted that the data might be confounded as C3G patients are generally younger at kidney failure, and thereby less likely to have comorbidities such as diabetes or hypertension apparent in the general CKD population.¹⁹ However, the expert also stressed that health impacts of kidney failure and dialysis treatment should not be discounted. The EAG hence decided to keep Lee 2005²⁴ utility values in its base-case and use Liem 2008²⁹ utility values for dialysis and post-transplant in a scenario analysis.

- b) The company used a mixed effects linear regression model for repeated measures to estimate CKD stage 1-4 utilities. It included subject-level random effects but no time variable, stating in response to clarification question B11 that the inclusion of fixed time effects on other covariates were minimal.⁴ The company further provided evidence supporting the normality assumption, yet demonstrated linearity only for the covariates age⁴ (Figure 8) and to a limited extent for baseline EQ-5D⁴ (Figure 9). Based on the mean EQ-5D scores over time by CKD stage⁴ (Figure 4), assuming a linear trend over time might be inappropriate. The EAG is concerned that time was included neither as a fixed nor random effect yet might be a confounding variable, biasing estimates and standard errors if subject-specific time trends and time-varying correlation were at present. However, the EAG agrees with the company that despite these weaknesses, expected differences seem minor. Further model specification, for instance with regard to slope shapes, interaction terms and variance-covariance structure would require more in-depth analyses and model fit assessments. Missing data of EQ-5D was up to 9% (baseline, Day 14 visit), assumed missing at random and not imputed. This level of missingness was deemed acceptable by the EAG. However, the EAG has no information on missing data of independent variables which would benefit from imputation despite EQ-5D at baseline.

- c) The EAG noticed the utility values for early CKD stages (Table 4.5) were relatively close to the UK general population one (0.92)¹ (Table 43). Upon inquiry, the company stated that early CKD stages present with little impact on HRQoL, which the EAG clinical expert agreed to for generally symptom-free CKD stages 1 and 2.¹⁹ Moreover, values were deemed similar to the (higher) ones from Jesky 2016²³ after age and sex adjustments, a study on general CKD in a substantially older population. From older and different CKD populations, TAs presented by the company in clarification response, Table 33⁴ had mostly lower utilities compared to the CS. The Adelphi DSP C3G study (N=385), which included 32 UK patients,³¹ reported EQ-5D-5L based on 100 observations from a cross-sectional survey which was open for 9 months.²² Utilities were derived using the US tariff and substantially lower. The study also showed unexpectedly increasing values for CKD stages 1-3A.⁴ (Table 30) The EAG is concerned about the considerable uncertainty surrounding early CKD stage utilities, and therefore requested a scenario analysis using the Adelphi DSP study which the company did not provide.

Moreover, the company pooled CKD stage 1 and 2 utility values since stage 1 utilities estimated by the mixed effects regression model were lower than stage 2 utilities. The EAG saw some shortcomings in this approach, as these stages report the highest number of measurements, underlying data issues might be masked or disease burden misrepresented. Upon inquiry, the company highlighted implausibility with regard to disease development and statistical non-significance of the slightly higher value of CKD stage 2 compared to 1 in the regression analyses (Table 41).¹ It also referred to previous NICE TAs in CKD which all pooled CKD stage 1 and 2.⁴ In light of the arguments provided by the company and the support by the independent clinical expert consulted by the EAG,¹⁹ the EAG agrees with the chosen approach.

- d) To assess the impact of pneumonia and sepsis, the company used a utility value on infections from Oppong 2013.²⁸ The authors reported a 0.156 utility difference from acute presentation of cough and lower respiratory tract infections to recovery at week 4 in 168 English patients, 50 years of

mean age, based on EQ-5D-3L. However, for the 181 Welsh patients of on average 53 years of age also included in the study, they reported a utility difference of 0.146. The EAG requested the company in clarification question B14⁴ to verify the chosen disutility value of 0.156 with additional literature, which the company did not provide. As impact is expected to be small, the EAG regards the uncertainty of this estimate a minor limitation.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, HS costs (healthcare resource utilisation [HCRU]: disease monitoring, transplant, and dialysis costs), vaccination and antibiotic costs, and event costs including: AE management costs, end of life costs, CV events (scenario analysis only) costs.

Where available, unit prices were based on the National Schedule of NHS costs (2023-24),³² the 2023/2024 drugs and pharmaceutical electronic marketing information tool (eMIT)³³, the 2023 Unit Costs of Health and Social Care,³⁴ and the British National Formulary (BNF).³⁵ Where unavailable, unit prices were sourced from literature.

Costs were inflated to the 2022/23 fiscal year using the NHS Cost Inflation Index (NHSCII) Pay and Price Index.³⁴

4.2.9.1 Resource use and costs data identified in the literature review

According to the CS, the cost and HCRU SLR identified six studies reporting HCRU in C3G. Out of these, the company did not consider any to provide relevant evidence for use in the submission, with reasons for not utilising each identified study provided in Appendix G, Table 9. As such, an additional targeted literature review (TLR) was conducted on NICE TAs in CKD with final guidance published in the last 10 years. Overall, 13 TAs were identified with HCRU sources for each summarised for CDK stages 1-4; CKD stage 5 (pre-KRT); dialysis; transplant (one-off); and post-transplant (long-term). CS Table 44 provides an overview of the HS cost sources utilised in the identified previous NICE TAs in CKDs.

4.2.9.2 Treatment acquisition costs (with Patient Access Scheme [PAS])

For the iptacopan + SoC arm, patients incurred costs of iptacopan in addition to the costs of background SoC therapies. Patients in the SoC comparator arm incurred the costs of SoC background therapies only. Provided all therapies are administered orally, no administration costs were included.

4.2.9.2.1 Iptacopan

In the CS, the cost of iptacopan was set to [REDACTED] (list price: £26,500) per 28-day pack, [REDACTED]. From here, a per annum cost was derived by calculating the average cost per day by dividing the pack price by the number of doses per pack.

4.2.9.2.2 SoC background therapies

For C3G, SoC could include ACEi/ARBs, MMF, CoS, and SGLT2is. Here, the proportion of patients receiving each of the components of SoC was derived from baseline characteristics in APPEAR-C3G and assumed equal for iptacopan + SoC and SoC. As per the CS, the specific ACEi/ARBs used to calculate costs reflect the most used treatments within these classes from the UK cohort of the Adelphi DSP study.³⁶ For treatments in the other SoC background therapy classes, the cheapest medication

within each class was selected. The price of dapagliflozin (SGLT2i) was sourced from the BNF. All other treatment prices were sourced from eMIT.

4.2.9.2.3 Dosage and pack sharing

Iptacopan and all SoC background therapies were administered orally. The cost per pack and dosages for each treatment were utilised to derive an acquisition cost per day and extrapolated out to calculate the cost per year. No pack sharing was factored into the economic model. Dosages and weighted treatment costs per day/year are presented in Table 4.6. No correction for missed doses was included in the economic model.

Table 4.6: Treatment dosage and weighted costs

Treatment	Class	Dose per day (mg)	Price per pack	Unit size (mg)	Units per pack	% patients	Weighted cost per day	Weighted cost per year
Iptacopan	N/A	200 b.i.d.	██████	200	56	N/A	██████	██████
SoC								
Ramipril	ACEi	10	£0.39	10	28	47.3%	£0.01	£2.41
Losartan	ARB	50	£0.39	50	28	52.7%	£0.01	£2.69
Dapagliflozin	SGLT2i	10	£36.59	10	28	5.4%	£0.07	£25.80
MMF	MMF	1,500	£6.45	500	50	36.5%	£0.14	£51.57
Prednisolone	CoS	7.5	£0.80	2.5	30	32.4%	£0.03	£9.47
Weighted cost							£0.25	£91.95
Based on CS, Table 45 and CS, Table 46 ¹ ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; b.i.d = twice daily; CoS = corticosteroid; CS = company submission; MMF = mycophenolate mofetil; N/A = not applicable; SGLT2i = sodium-glucose co-transporter 2 inhibitor								

4.2.9.3 HS costs

HS costs reflect HCRU for disease monitoring (nephrologist monitoring visits; per visit disease monitoring tests) and, for KRT HSs, transplant and dialysis costs.

4.2.9.3.1 Monitoring costs

Outpatient resource use was derived from a survey of UK clinicians participating in an advisory board.¹² Clinician inputs were averaged to derive economic model inputs. Monitoring visits per HS and per visit disease monitoring tests and unit costs are presented in CS, Table 47 and Table 48, respectively.

4.2.9.3.2 Dialysis and (post-)transplant costs

The one-time cost of kidney transplant was taken as a weighted average for living donor transplant and deceased donor transplant. The proportion of patients receiving a living or deceased donor transplant was derived from RaDaR data in patients with C3G. Transplants were costed using 2023/2024 NHS reference costs.³² Post-transplant costs comprised annual costs for immunosuppression medication, based on an NHS Blood and Transplant fact sheet.³⁷

The costs of dialysis were included using 2023/2024 NHS reference costs, taking a weighted average dialysis cost for continuous ambulatory peritoneal dialysis (CAPD), automated PD, and HD (and transportation for patients on in-centre HD). Proportions were derived from RaDaR data in patients with C3G. HD was assumed to be repeated three times per week with CAPD and APD carried out daily. In-centre HD transport costs were derived from Liu 2015.³⁸ The proportion of patients receiving in-centre HD was derived from total activity reported in the 2023/2024 NHS reference costs.

HS costs presented in Table 4.7 are comprised of costs taken from CS, Tables 47, 48, and 50.

Table 4.7: Health state costs

Health state	Weighted one-off HS costs	Weighted cost per annum	References	Justification
CKD stage 1	N/A	£442.84	CS, Tables 47, and 48	Two monitoring visits*
CKD stage 2	N/A	£442.84	CS, Tables 47, and 48	Two monitoring visits*
CKD stage 3a	N/A	£664.26	CS, Tables 47, and 48	Three monitoring visits*
CKD stage 3b	N/A	£885.68	CS, Tables 47, and 48	Four monitoring visits*
CKD stage 4	N/A	£1,107.10	CS, Tables 47, and 48	Five monitoring visits*
CKD stage 5 (pre-KRT)	N/A	£1,107.10	CS, Tables 47, and 48	Five monitoring visits*
Dialysis	N/A	£42,901.87	CS, Tables 47, 48, and 50	Annual costs: three monitoring visits*; weighted average dialysis costs (CAPD, APD, HD); weighted transport for in-centre HD**
Transplant	£33,083.31	£8,119.33	CS, Tables 47, 48, and 50	One-off cost: weighted average for living donor transplant and deceased donor transplant. Annual costs: four monitoring visits*; post-transplant costs (immunosuppression) for all patients

Based on CS Table 47, CS, Table 48, CS, Table 50¹

* Annual frequency of monitoring visits and resource use per visit from UK clinician advisory board.

** 96.8% of HD patients receiving in-centre HD.

APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; CKD = chronic kidney disease; CS = company submission; HD = haemodialysis; HS = health state; KRT = kidney replacement therapy; N/A = not applicable; UK = United Kingdom

4.2.9.4 *Vaccination and antibiotic costs*

As per the summary of product characteristics (SmPC), patients receiving iptacopan must be vaccinated against *N. meningitidis* and *S. pneumoniae*, with vaccination against *H. influenzae* type B recommended. All patients in the economic model on iptacopan receive vaccinations for *N. meningitidis* and *S. pneumoniae* every 5 years (modelled as 0.2 per year), and one vaccination for *H. influenzae* type B at the start of iptacopan treatment. Vaccination costs were sourced from the BNF. As per UK clinicians, the cost of prophylactic antibiotics (penicillin) was also included for all iptacopan patients (CS, Table 51).

4.2.9.5 *Event costs*

4.2.9.5.1 *Adverse event costs*

The inclusion and distribution of AEs in the economic model are described in Section 4.2.7 of the EAG report. To cost AEs in the economic model, a weighted average unit cost was derived using 2023/24 NHS reference costs for lobar, atypical and viral pneumonia (HRG codes DZ11K-DZ11V), bronchopneumonia (HRG codes DZ23H-DZ23N), and sepsis (HRG codes WJ06A-WJ06J). Costs were weighted based on total activity in the NHS reference costs. The total weighted average unit cost per AE utilised in the economic model was £2,819.03.

4.2.9.5.2 *End-of-life costs*

End-of-life costs (one-off cost upon entering the death state) were modelled as the hospital costs for terminal care in the 30 days prior to death. These were taken from Kerr 2016,³⁹ which reported end-of-life care in CKD in England and aligned with the approach taken in TA937.⁴⁰

4.2.9.5.3 *Cardiovascular event costs (scenario analysis only)*

CV events were included in a scenario analysis only. The costs associated with stroke and myocardial infarction were sourced from 2023/24 NHS reference costs and TA942.⁴¹ An acute cost per event (stroke: £7,172.71; myocardial infarction: £3,522.51) and annual post-event cost (stroke: £1,303.78; myocardial infarction: £893.41) were included as a one-off cost weighted by the proportion of patients experiencing an event in each cycle.

EAG comment: The main concerns of the EAG relate to: a) wastage costs at iptacopan discontinuation; b) misalignment between inflated costs and costs informed by National Schedule for NHS Costs; c) reproducibility of (post-)transplant and dialysis, and SAE costs.

- a) In the CS, acquisition cost calculations assumed no waste. That is, per pack costs were used to derive an average cost per daily dose. Provided each pack of iptacopan (200 mg) contained 56 capsules to be taken b.i.d. ~3.26 packs are required (and initially modelled) per 3-month model cycle. This is likely to underestimate iptacopan acquisition costs. The NICE process and methods guide states that the costs of oral treatments dispensed in tablet packs should be evaluated on a per-pack basis, unless clinical experts or other evidence suggests that prescribing and dispensing is done such that there would be no wastage. Clarification question B15 requested an updated economic model and scenario analysis taking a per-pack costing approach. In response, the company provided the updated their base-case results modelling an additional ~0.74 packs to the total acquisition cost of iptacopan (i.e., modelling four packs in a patient's last model cycle on treatment), accounting for tablets not used upon treatment discontinuation. This scenario resulted in an increase in incremental costs of [REDACTED] and an increased (deterministic) ICER from [REDACTED] to [REDACTED] ([REDACTED]). The

EAG favours the incorporation of wastage costs associated with iptacopan acquisition and therefore adopts this scenario in its base-case. Additionally, the EAG extended this approach to also apply to all SoC therapies in both arms.

- b) The CS inflated costs to the 2022/23 fiscal year using the NHSCII Pay and Price index. Provided 2023 edition of the Personal Social Services Research Unit (PSSRU) Cost of Health and Social Care Manual was the latest version at the time of submission, the EAG noted a slight misalignment between inflated costs and costs derived from the National Schedule of NHS Costs 2023/2024. The EAG is satisfied with the company's justification that the approach takes the most recent information possible, despite the resulting misalignment. The impact on results in the economic model is likely to be very small.
- c) For reproducibility purposes, clarification questions B16 and B17 requested further detail regarding the calculation of (post-) transplant and dialysis costs, and cost of SAEs related to iptacopan, respectively. In response, the company provided a clear overview of how these costs were calculated within the economic model, which are now reproducible for the EAG. The EAG is therefore satisfied with the response provided by the company.

4.2.10 Disease severity

In the CS economic model, the company calculated absolute and proportional quality-adjusted life year (QALY) shortfall using a starting age of 27.9 years (APPEAR-C3G), proportion of females of 36.49% (APPEAR-C3G), expected QALYs with SoC of 15.13 (derived from economic model results), and expected QALYs without the condition of 21.00 (derived from England and Wales life tables from the Office for National Statistics (ONS)⁴² and general population utility values for the UK reported by Hernandez-Alava 2022) APPEAR-C3G.^{25, 27} Results of the company's QALY shortfall analysis are summarised in Table 4.8.

Table 4.8: Summary of company QALY shortfall analysis

Expected total QALYs for the general population	Total expected QALYs for people with C3G on current SoC	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
21.00	15.13	5.87	0.28	1.0
Based on Table 53 in CS ¹ C3G = complement 3 glomerulopathy; CS = company submission; QALY = quality-adjusted life year; SoC = standard of care				

EAG comment: Both the absolute and proportional shortfall resulted in a QALY weight of x1.0. The EAG was able to reproduce the QALY weight using the Schneider 2021⁴³ QALY shortfall calculator (online web tool)

5. Cost effectiveness results

5.1 Company's cost effectiveness results

The CS base-case cost effectiveness results (probabilistic) at the PAS price included in the CS amount to incremental costs of iptacopan + SoC versus SoC of [REDACTED], incremental life years (LYs) of 0.48, and incremental QALYs of 1.71. The resulting ICER amounted to [REDACTED] per QALY gained. The incremental net health benefit (iNHB) for iptacopan + SoC versus SoC was [REDACTED] and [REDACTED] QALYs at £20,000 and £30,000 willingness-to-pay (WTP) thresholds, respectively (see Table 5.1). The company updated its base-case following clarification questions to iptacopan wastage costs at discontinuation. The updated company base-case results are reported in section 6.

Table 5.1: Summary of the initial company pairwise deterministic and probabilistic results

Treatment	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)	iNHB at £20,000	iNHB at £30,000
Probabilistic							
SoC	£351,750	15.17	-	-	-	-	-
Iptacopan + SoC	[REDACTED]	16.88	[REDACTED]	1.71	[REDACTED]	[REDACTED]	[REDACTED]
Deterministic							
SoC	£355,162	15.13	-	-	-	-	-
Iptacopan + SoC	[REDACTED]	16.88	[REDACTED]	1.74	[REDACTED]	[REDACTED]	[REDACTED]
Based on Tables 58 and 60 of the CS ¹ CS = company submission; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life year; SoC = standard of care							

Overall, the technology is modelled to affect QALYs by:

- Increased time to disease progression with incremental QALYs in CKD stage 1-4 of 4.93 (283% of total deterministic incremental QALYs).

Overall, the technology is modelled to affect costs by:

- Increased acquisition costs (with PAS) in iptacopan + SoC arm (increased costs of [REDACTED], [REDACTED] of the total deterministic incremental costs).

The modelling assumptions that have the greatest effect on the ICER are:

- The assumption that the iptacopan before-after comparison using APPEAR-C3G including the open-label extension study is reflective of treatment effectiveness in UK clinical practice. The upper (10.39) and lower (3.48) parameter values of the (deterministic) one-way sensitivity analysis of iptacopan treatment effectiveness resulted in ICERs of [REDACTED] and [REDACTED], respectively.

EAG comment: The main concerns of the EAG relate to: a) observed versus extrapolated gains in costs and QALYs, and b) lack of provision of time to CKD data for the iptacopan + SoC arm.

- a) Clarification question B20 requested an overview of the total costs and QALYs accrued within the economic model in the observed versus extrapolated period per treatment arm. These were provided, however with the caveat for direct comparisons being that the observed period was 2.5 years for SoC (maximum duration of pre-iptacopan data informing the eGFR slope) and 2.0 years for iptacopan (maximum duration of on-iptacopan data informing the eGFR: APPEAR-C3G + extension study). For the iptacopan + SoC arm, 10.25% of total QALYs and [REDACTED]% of total costs were accrued in the observed period. For the SoC arm, 14.01% of total QALYs and 0.94% of total costs were accrued in the observed period. As such, a higher proportion of total QALYs and a lower proportion of total costs were accrued in the extrapolated period for iptacopan + SoC, despite the observed period being 0.5 years shorter than in the SoC arm. Furthermore, the EAG noted that the majority of incremental QALYs and costs are also accumulated beyond the observed period. This highlights the substantial extrapolation benefit for the iptacopan versus SoC arm. Given the uncertainty regarding the long-term extrapolation of treatment effect (EAG report Section 4.2.6), the EAG would like to see explanation as to the mechanism by which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence.
- b) CS, Appendix H, Table 3 presented kidney survival per treatment arm at 5 years and 10 years, as well as the median time (years) to kidney failure. The EAG requested (clarification question B 19) the table to be expanded to include kidney survival at time points 1, 2, 3, 4, 5, 10, 15, and 20 years, and to capture the time to each CKD stage. Time to next stage was provided for each CKD stage for the SoC arm, however, was not provided for the iptacopan + SoC arm. For comparability with SoC, the EAG would like to also see the time to each CKD stage for the iptacopan + SoC arm.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses. The probabilistic CS base-case analyses indicated cost effectiveness probabilities of [REDACTED]% at WTP thresholds of £20,000 and £30,000 per QALY gained. DSA showed that the results were most sensitive to changes in analysis approach taken to model iptacopan treatment effect, and the age and constant coefficients utilised in the APPEAR-C3G utility linear regression model. The company conducted several scenario analyses. The results showed ICERs ranging between [REDACTED] and [REDACTED] per QALY gained. The three most influential scenarios that increased the ICER were 3) eGFR slope data from APPEAR-C3G placebo comparison (based on 6 months of data), 5) CKD stage transitions at upper eGFR bound of CKD stage, and 2) eGFR slope data from pooled population (APPEAR-C3G and Phase 2 native kidney cohort; up to 4.7 years iptacopan treatment duration).

EAG comment: The main concern of the EAG relates to the inclusion of HSUV parameters within the PSA.

- a) Health state utility values (HSUVs) for CKD stages 1-4 (i.e., trial utilities) were not varied in the PSA. Clarification question B-21 requested justification for the exclusion of HSUV. In response, the company suggest that these were implicitly included as the parameters utilised in the linear regression model to derive utilities were varied using a Cholesky decomposition distribution. However, HSUV calculations in the economic model seem not to be linked to the probabilistically varied parameters but instead to a separate table (model sheet "Control", cells BF22:BF26) with

linear regression model parameters hard coded to the cells. That is, no result changes were observed by the EAG when setting linear regression model parameters to not be varied in the PSA. Further, post-transplant and dialysis HSUVs were not varied within the PSA. Therefore, the EAG varied HSUVs in the model directly in its analyses by assigning a beta distribution to HSUVs. Upper and lower parameter values were assumed to be +/- 20% of the deterministic input for trial HSUVs, and calculated using the 95% CI for post-transplant and dialysis HSUVs. This was included as a “fixing error” in the EAG analyses.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The company held two advisory board meetings with nine (April 2022) and 10 (November 2024) UK clinicians experienced with C3G. Discussion points were the current SoC and the C3G treatment landscape, the level of unmet need, iptacopan trial data, modelling disease progression and disease management before and after kidney failure.

Additional calls occurred separately with two clinicians on uncertainty within the CS, in particular surrounding the eGFR-based modelling approach. A joint call involving one clinical and external health economic expert addressed model validation, i.e., base-case selection for disease progression and treatment effect, HSUVs and costs, AEs, and clinical outputs of the draft economic model.

5.3.2 Technical verification

An independent team of health economic experts not involved in model development assessed the model with a quality control and internal validation checklist, based on the published TECH-VER checklist.⁴⁴ An independent analyst performed a full input quality check against original sources.

5.3.3 Comparisons with other TAs

Cross-validation with other TAs was not explicitly mentioned in the CS, Section B3.13.

5.3.4 Comparison with external data used to develop the economic model

Validation of external data used to develop the economic model was not explicitly mentioned in the CS, Section B3.13.

5.3.5 Comparison with external data not used to develop the economic model

Cross-validation with external data not used to develop the economic model was not explicitly mentioned in the CS, Section B3.13.

EAG comment: The main concerns of the EAG relate to: a) no access to minutes of advisory board meetings, b) technical verification, and c) cross validation.

- a) Various modelling assumptions in the CS were justified based on expert opinion from advisory board meetings and consultations. The EAG noted however, that only summaries rather than full meeting minutes of these were provided, although requested in clarification question B23. The EAG considers this to be a serious transparency issue as it is unable to verify various assumptions made by the company, and the full meeting details should therefore be provided.

- b) The EAG asked for more details on technical verification in clarification question B24. The company provided internal validation and quality control checklists,⁴⁵⁻⁴⁷ which included a comprised version of the TECH-VER checklist but not the full TECH-VER checklist⁴⁴ despite a request by the EAG.⁴ However, the provided checklists seemed sufficient to the EAG to ensure smooth model performance.
- c) The EAG asked for more detailed cross validation in clarification questions B25 and B26. The company performed a comprehensive TLR of NICE TAs due to a lack of published cost effectiveness studies in C3G, capturing the last 10 years. Although no TA addressed C3G specifically, the TLR informed economic model development and input values. The company provided a cross validation of modelling features, comparing them with previous studies and explaining differences. Although acknowledging the disease's rarity, the EAG is concerned that external validity might be threatened as the previous TAs “covered different diseases, interventions, comparators, and time horizons, and as such a comparison of outcomes with previous appraisals [...] [was] not considered meaningful” by the company.

6. EAG's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm 2020:⁴⁸

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the DP and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016):

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

1. Inclusion of CKD stages 1-4 utility values in sensitivity analyses.
Calculating standard deviations and assigning beta distributions to CKD stages 1-4 utility values for inclusion in sensitivity analyses.

6.1.1.2 Fixing violations

2. Inclusion of wastage costs at iptacopan and SoC discontinuation (Section 4.2.9)

Modelling a total of four packs in the patient's last model cycle on treatment to account for wastage costs resulting from discontinuation.

6.1.1.3 Matters of judgement

3. Use of RaDaR baseline patient characteristics (Section 4.2.3).
Using baseline patient characteristics from RaDaR instead of the APPEAR-C3G trial to inform the economic model.
4. Use of RaDaR data and the randomised comparison in APPEAR-C3G to inform eGFR slopes (Section 4.2.6).
Estimating the eGFR slope for SoC based on RaDaR and subsequently applying the iptacopan treatment effect from the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope.
5. Modelling of severe AEs (Section 4.2.7)
Modelling all grade 3+ AEs based on the controlled safety set irrespective of a suspected relationship with iptacopan.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

6. Use of randomised comparison in APPEAR-C3G to inform eGFR slopes (Section 4.2.6).
Estimating the eGFR slope for SoC and iptacopan using data from the randomised double-blind period of APPEAR-C3G.
7. Use of Liem 2008 to inform dialysis and post-transplant utility values (Section 4.2.8).
Informing dialysis and post-transplant utility values based on Liem 2008 instead of Lee 2005.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on FEs highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Data used to generate eGFR slopes	4.2.6	Methods	Use RaDaR data or pre-iptacopan data to inform SoC, and apply the iptacopan treatment effect based on the randomised comparison to inform iptacopan.	+	Yes	N/A
Assumption of a constant, CKD-stage independent speed of progression	4.2.6	Methods and bias & indirectness	Using CKD stage-dependent and time-dependent eGFR decline rates from the iptacopan trials in C3G.	+/-	No	Analyses using CKD stage-dependent and time-dependent eGFR decline rates as requested above, potentially informed by other literature/external data if not deemed feasible based on APPEAR-C3G.
Modelling of treatment discontinuation	4.2.6	Methods and bias & indirectness	Exploring alternative, time-varying discontinuation rates. Exploring TTD analyses.	+/-	No	Full details of the TTD model selection process based on the NICE DSU TSD 14 guidance.
Assumption of a constant iptacopan treatment effect over the model time horizon while patients remained on treatment	4.2.6	Methods and bias & indirectness	Further justification and analyses to assess the assumption of a constant treatment effect during the observed period. Scenario analyses exploring treatment waning beyond the observed period.	+	No	Further justification and analyses to assess the assumption of a constant treatment effect during the observed and beyond the observed period as requested above.

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
(Face) validity of the chosen CKD stage 5+ utilities	4.2.8	Bias & indirectness	The use of Liem 2008 and Sinha 2025 utility values. A more detailed overview of relevant TAs to cross-validate utilities.	+	Partly	Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients.
Majority of QALYs and costs accumulated beyond the observed data	5.1	Transparency	None.	+/-	No	Additional explanation as to the mechanism by which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence.
Lack of transparency regarding expert consultation	5.3	Transparency	Provide the full advisory board meeting minutes.	+/-	No	Provide the full advisory board meeting minutes.
^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator. ^b Explored. C3G = complement 3 glomerulopathy; CKD = chronic kidney disease; DSU = Decision Support Unit; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; EQ-5D = European Quality of Life-5 Dimensions; FEs = Fixing errors; ICER = incremental cost effectiveness ratio; N/A = not applicable; NICE = National Institute for Health and Care Excellence; QALYs = quality-adjusted life years; RaDaR = National Registry of Rare Kidney Diseases; SoC = standard of care; TAs = Technology Assessments; TSD = Technical Support Document; TTD = time to treatment discontinuation						

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the “EAG” sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic/probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Deterministic							
CS base-case							
SoC	£355,162	15.13	-	-	-	-	-
Iptacopan + SoC	████████	16.88	████████	1.74	████████	██████	██████
Fixing error (1 - [probabilistic analyses only] include CKD stage 1-4 utilities in PSA)							
Fixing violation (2 - per pack costing approach for iptacopan and SoC therapies)							
SoC	£355,192	15.13	-	-	-	-	-
Iptacopan + SoC	████████	16.88	████████	1.74	████████	██████	██████
Matter of Judgement (3 - population baseline characteristics from RaDaR)							
SoC	£390,532	14.57	-	-	-	-	-
Iptacopan + SoC	████████	16.23	████████	1.66	████████	██████	██████
Matter of Judgement (4 - eGFR slope based on RaDaR for SoC, apply double blind treatment effect for iptacopan)							
SoC	£288,267	15.70	-	-	-	-	-
Iptacopan + SoC	████████	16.86	████████	1.16	████████	██████	██████
Matter of Judgement (5 - all grade 3+ AEs from controlled safety set)							
SoC	£359,350	15.11	-	-	-	-	-
Iptacopan + SoC	████████	16.85	████████	1.74	████████	██████	██████
EAG base-case							
SoC	£292,470	15.68	-	-	-	-	-
Iptacopan + SoC	████████	16.84	████████	1.16	████████	██████	██████
Probabilistic							
CS base-case							
SoC	£355,352	15.15	-	-	-	-	-

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Iptacopan + SoC		16.69		1.54			
Fixing errors (1 - [probabilistic analyses only] include CKD stage 1-4 utilities in PSA)							
SoC	£355,352	15.15	-	-	-	-	-
Iptacopan + SoC		16.69		1.54			
Fixing violation (2 - per pack costing approach for iptacopan and SoC therapies)							
SoC	£355,382	15.15	-	-	-	-	-
Iptacopan + SoC		16.69		1.54			
Matter of Judgement (3 - population baseline characteristics from RaDaR)							
SoC	£391,534	14.58	-	-	-	-	-
Iptacopan + SoC		16.05		1.47			
Matter of Judgement (4 - eGFR slope based on RaDaR for SoC, apply double blind treatment effect for iptacopan)							
SoC	£292,779	15.65	-	-	-	-	-
Iptacopan + SoC		16.82		1.17			
Matter of Judgement (5 - all grade 3+ AEs from controlled safety set)							
SoC	£359,524	15.13	-	-	-	-	-
Iptacopan + SoC		16.67		1.54			
EAG base-case							
SoC	£296,967	15.63	-	-	-	-	-
Iptacopan + SoC		16.80		1.17			
AE = adverse event; CKD = chronic kidney disease; CS = company submission; EAG = External Assessment Group; eGFR = epidermal growth factor receptor; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = Net Health Benefit; PSA = probabilistic sensitivity analysis; QALY = quality adjusted life year; RaDaR = National Registry of Rare Kidney Diseases; SoC = standard of care							

Table 6.3: Deterministic/probabilistic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Deterministic							
EAG base-case							
SoC	£292,470	15.68	-	-	-	-	-
Iptacopan + SoC		16.84		1.16			
Scenario Analysis (6 - eGFR slope based on randomised comparison from APPEAR-C3G)							
SoC	£416,110	14.33	-	-	-	-	-

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Iptacopan + SoC	████████	15.88	████████	1.55	████████	██████	██████
Scenario Analysis (7 - dialysis and post-transplant KRT utilities based on Liem 2008)							
SoC	£292,470	16.62	-	-	-	-	-
Iptacopan + SoC	████████	17.43	████████	0.81	████████	██████	██████
Probabilistic							
EAG base-case							
SoC	£296,967	15.63	-	-	-	-	-
Iptacopan + SoC	████████	16.80	████████	1.17	████████	██████	██████
Scenario Analysis (6 - eGFR slope based on randomised comparison from APPEAR-C3G)							
SoC	£418,318	14.32	-	-	-	-	-
Iptacopan + SoC	████████	15.77	████████	1.46	████████	██████	██████
Scenario Analysis (7 - dialysis and post-transplant KRT utilities based on Liem 2008)							
SoC	£296,967	16.58	-	-	-	-	-
Iptacopan + SoC	████████	17.39	████████	0.82	████████	██████	██████
C3G = complement 3 glomerulopathy; EAG = External Assessment Group; eGFR = epidermal growth factor receptor; HD = haemodialysis; ICER = incremental cost-effectiveness ratio; Incr. = incremental; KRT = kidney replacement therapy; NHB = Net Health Benefit; PD = peritoneal dialysis; QALY = quality adjusted life year; SoC = standard of care							

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was £████████ per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of █% at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustment was estimating the eGFR slope for SoC based on RaDaR data and subsequently applying the iptacopan treatment effect from the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope. The ICER increased most in the scenario analysis with alternative assumptions regarding KRT utilities.

6.4 Conclusions of the cost effectiveness Section

The CS, Appendices E F and G, and response to clarification^{1, 4, 13, 14} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use in C3G. The searches for economic evidence were conducted on 16 September 2020 and updated on 10 October 2024. The searches for healthcare resource use were conducted on 11 February 2021 and updated on 10 October 2024. HRQoL searches were conducted on 22 January 2021 and updated on 12 November 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases, HTA websites and other grey literature resources were searched. Overall, the EAG has no concerns about the literature searches conducted.

The company's cost effectiveness model complied with the NICE reference case. The most prominent issues highlighted by the EAG are reported in the key issue tables in Section 1.5.

Firstly, the company's approach of estimating eGFR slopes was suboptimal. Using a before-after comparison (i.e., pre-iptacopan data for SoC and on-iptacopan data for iptacopan) based on APPEAR-C3G and the open-label extension study rather than using the randomised double-blind period of APPEAR-C3G is prone to biasing the estimated eGFR slopes. The EAG concluded that the approach of estimating the eGFR slope for SoC based on RaDaR and subsequently applying the iptacopan treatment effect from the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope to be the most reasonable for (relative) treatment effectiveness in the economic model. Secondly, several assumptions were made regarding the time independence of various parameters over the modelled time horizon. There was substantial uncertainty related to the assumption that the speed of eGFR progression was independent of the CKD stage and constant over time. Such an assumption could lead to either overestimation or underestimation of the progression speed, which in turn would have substantial implications for the long-term modelling of costs and effects, particularly those associated with kidney replacement therapies such as dialysis and kidney transplantation. Next to that, the rate of discontinuation from iptacopan treatment was assumed to be constant over time. This assumption was questioned by the EAG and its clinical expert, who indicated that the discontinuation rate over subsequent years remains uncertain. The EAG preferred using parametric survival modelling based on TTD to inform this aspect of the economic model. The impact of these analyses may be more pronounced when combined with assumptions related to waning of the iptacopan treatment effect. A more detailed explanation of the TTD model selection process, as per NICE DSU TSD 14 guidance, is necessary for a comprehensive assessment. Furthermore, the assumption of a constant iptacopan treatment effect over the model time horizon was also scrutinised. Despite assertions from the company and the EAG clinical expert that the *"on-target effect on complement inhibition will remain comparable throughout"*, this assumption was deemed insufficiently assessed. Additional evidence demonstrating a constant treatment effect during the observed period, along with scenario analyses exploring potential treatment waning beyond the observed period, would be valuable in addressing this critical issue. Thirdly, CKD stage 5+ utility values were considered relatively low, potentially resulting from age-related comorbidities in the older, wider CKD population that was used to inform these utility values in the economic model. Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients might help to resolve this key issue. Fourthly, the EAG noted that the majority of absolute and incremental QALYs and costs for iptacopan + SoC and SoC were accumulated beyond the observed data period, requiring explanation as to the mechanism by which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence. Finally, the company did not provide the full advisory board report, which was considered a serious transparency issue as it hinders validation of various modelling assumptions informed by clinical experts.

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was £[REDACTED] per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [REDACTED]% at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustment was estimating the eGFR slope for SoC based on RaDaR and subsequently applying the iptacopan treatment effect from the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope. The ICER increased most in the scenario analysis with alternative assumptions regarding KRT utilities.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of iptacopan + SoC, which can be partly resolved by the company. This includes providing CKD stage-

dependent and time-dependent eGFR decline rates, full details of the TTD model selection process based on the NICE DSU TSD 14 guidance, analyses to assess the assumption of a constant treatment effect during and beyond the observed period, analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients, explanation and justification of the mechanisms by which the economic model generated a substantial proportion of QALYs and costs beyond the observed data, and providing the full advisory board meeting minutes. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of iptacopan + SoC compared with SoC.

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in collaboration with:

Erasmus School of
Health Policy
& Management



Maastricht University

Iptacopan for treating complement 3 glomerulopathy [ID6283]

ADDENDUM

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Confidential (CON) data are highlighted in blue throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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Contributions of authors:

Huiqin Yang acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong also acted as project lead as well as health economist on this assessment and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Teresa Holly, Bradley Sugden, and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Xiaoyu Tian acted as systematic reviewers as well as health economists on this assessment. Huiqin Yang and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Background to addendum

Following the factual inaccuracy check, the company provided an updated economic model including a [REDACTED].

Additionally, modelling errors and inaccuracies by both the company and EAG were identified, including:

- EAG_1 became obsolete following the company's fix of lacking CKD stage 1-4, post-transplant and dialysis HSUVs in the PSA. CKD stage 1-4 HSUVs are now varied through parameters to the linear regression analyses, rather than directly.
- The button "Sensitivity analysis!B10:C10" is not working properly, and thus the EAG used "Control!C2" alternatively to perform the identical action of updating parameters before a probabilistic analysis run. Additionally, within the updated economic model, cell G2 in the Control tab used the "COUNT" formula to determine the number of inputs to iterate over within the PSA. This has been updated to "COUNTA" to avoid the exclusion of non-numeric cells (specifically, the constant value in the utility linear regression now included in the PSA).
- Wastage costs for SoC therapies at discontinuation are now weighted by the proportion patients receiving each treatment (EAG_2).
- For EAG_6 (scenario analysis), "Analysis 3" (rather than "Analysis 1") is now selected in cell C7 in the Clinical Data tab.

This addendum provides updated EAG results including the company's updated iptacopan price and including fixes for the modelling errors and inaccuracies above.

Table 1: Corrected deterministic/probabilistic EAG base-case including updated company price

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Deterministic							
CS base-case							
SoC	£355,162	15.13	-	-	-	-	-
Iptacopan + SoC		16.88		1.74			
Fixing Error (1 – Inclusion of HSUVs in PSA) – Fixed in company base case post-FAC							
Fixing violation (2 - per pack costing approach for iptacopan and SoC therapies)							
SoC	£355,164	15.13	-	-	-	-	-
Iptacopan + SoC		16.88		1.74			
Matter of Judgement (3 - population baseline characteristics from RaDaR)							
SoC	£390,532	14.57	-	-	-	-	-
Iptacopan + SoC		16.23		1.66			
Matter of Judgement (4 - eGFR slope based on RaDaR for SoC, apply double blind treatment effect for iptacopan)							
SoC	£288,267	15.70	-	-	-	-	-

[illegible]

Table 2: Corrected probabilistic scenario analysis including updated company price (conditional on EAG base-case).

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (£20,000)	NHB (£30,000)
Deterministic							
EAG base-case							
SoC	£292,443	15.68	-	-	-	-	-
Iptacopan + SoC		16.84		1.16			
Scenario Analysis (6 - eGFR slope based on randomised comparison from APPEAR-C3G)							
SoC	£244,820	16.25	-	-	-	-	-
Iptacopan + SoC		17.68		1.43			
Scenario Analysis (7 – Dialysis and post-transplant KRT utilities based on Liem et al. (2008))							
SoC	£292,443	16.62	-	-	-	-	-
Iptacopan + SoC		17.43		0.81			
Probabilistic							
EAG base-case							
SoC	£296,180	15.65	-	-	-	-	-
Iptacopan + SoC		16.81		1.16			
Scenario Analysis (6 - eGFR slope based on randomised comparison from APPEAR-C3G)							
SoC	£195,134	17.07	-	-	-	-	-
Iptacopan + SoC		18.05		0.98			
Scenario Analysis (7 – Dialysis and post-transplant KRT utilities based on Liem et al. (2008))							
SoC	£296,180	16.59	-	-	-	-	-
Iptacopan + SoC		17.40		0.81			
C3G = complement 3 glomerulopathy; EAG = External Assessment Group; eGFR = epidermal growth factor receptor; HD = haemodialysis; ICER = incremental cost-effectiveness ratio; Incr. = incremental; KRT = kidney replacement therapy; NHB = Net Health Benefit; PD = peritoneal dialysis; QALY = quality adjusted life year; SoC = standard of care							

Single Technology Appraisal

Iptacopan for treating complement 3 glomerulopathy [ID6283]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 11 June 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink

Section 1: Factual inaccuracies related to EAG's key issues

Key Issues 1, 2, 3: Key issues regarding the decision problem and eculizumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, Section 1.3 "The DP addressed in the company submission (CS) is broadly in line with the Final Scope issued by NICE. However, there is a lack of evidence on adult patients (Table 1.2) as well as on certain comparators (Table 1.3)."	"The DP addressed in the company submission (CS) is broadly in line with the Final Scope issued by NICE. However, there is a lack of evidence on adult patients (Table 1.2) as well as on certain comparators (Table 1.3)."	All evidence presented in the CS is in adult patients, and Table 1.2 does not mention a lack of evidence in adult patients; therefore, this note should be removed or amended.	Amended.
Page 12, Section 1.3, Table 1.2 "The EAG requested a subgroup analysis, in line with the NICE scope, to which the company stated that, although the Phase 2 trial included a cohort of patients with post-transplant recurrence of C3G, "...the trial was single-arm and the sample size was considered too small (N=11) to robustly inform economic modelling in a post-transplant subgroup. Therefore, the economic analyses presented are based on data in native kidney patients. Given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native	"The EAG requested a subgroup analysis for the cohort of patients with highly aggressive post-transplant recurrence who would receive eculizumab, in line with the NICE scope, to which the company stated that, although the Phase 2 trial included a cohort of patients with post-transplant recurrence of C3G, to which the company provided a response detailing why this was not feasible. The company submission stated in relation to the Phase 2 trial and post-transplant cohort: "...the trial was single-arm and the sample size was considered too small (N=11) to robustly inform economic modelling in a post-transplant subgroup. Therefore, the economic analyses presented are based on data in native	The quoted text included in the EAG report was not provided in response to an EAG request but included in the original CS. While the EAG requested a subgroup analysis, this was not for the post-transplant cohort, but for the small number of patients within this cohort with highly aggressive disease who would be eligible for eculizumab under the NHS England clinical commissioning policy, to which the company provided a full response (clarification questions [CQ] A3, A11).	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>kidney patients are considered transferable to transplanted patients.”</i>	<i>kidney patients. Given that the underlying disease mechanism is the same in native kidney and post-transplant recurrent C3G, UK clinicians advised that iptacopan data in native kidney patients are considered transferable to transplanted patients.”</i>		
Page 12, Section 1.3, Table 1.2 “This would imply that the C3G recurrence post-transplant subgroup is included in the DP population even if there are no data to inform clinical effectiveness in this subgroup.”	“This would imply that the C3G recurrence post-transplant subgroup is included in the DP population even if there are no comparative data to inform clinical effectiveness in this subgroup.”	Data to inform clinical effectiveness of iptacopan in the subgroup with post-transplant recurrence are available from the single-arm Phase 2 study, as presented in Section 2.5.1.4 and Section 2.5.2.2 of the CS.	Amended.
Page 24, Section 2, Table 2.1 “No evidence has been presented to demonstrate the effectiveness of iptacopan in the C3G recurrence post-transplant subgroup or the small subgroup of those eligible for eculizumab (>20% decline in eGFR) within the previous 3 months).”	“No comparative evidence has been presented to demonstrate the effectiveness of iptacopan in the C3G recurrence post-transplant subgroup or the small subgroup of those eligible for eculizumab (>20% decline in eGFR) within the previous 3 months).”		Amended.
Page 13, Section 1.3, Table 1.3 “They went on to argue that eculizumab is of reduced relevance in light of the fact that iptacopan would be delivered at an earlier point in the care pathway given that NHS England criteria require evidence of a significant decline of transplant function (>20% decline in eGFR) within the	“They went on to argue that eculizumab is of reduced relevance in light of the fact that eculizumab use is extremely limited in UK clinical practice (~1 patient per year on average) and that iptacopan would be delivered at an earlier point in the care pathway given that NHS England criteria require evidence of a significant decline of transplant function (>20%	Since this statement summarises the company’s arguments (“they” refers to “the company”) all key elements of the company’s rationale need to be reflected (see CS Table 1 and CQ response A3).	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
previous 3 months before eculizumab can be initiated.”	decline in eGFR) within the previous 3 months before eculizumab can be initiated.”		
Page 29, Section 2.3 As above	As above		Amended.
Page 13, Section 1.3, Table 1.3 “This might indicate that, if recurrent C3G post-transplant patients were treated with iptacopan then they would never become eligible for eculizumab, which would rule it out as a comparator, but if any were treated with current ECM then they might.”	“This might indicate that, if recurrent C3G post-transplant patients were treated with iptacopan then they would never become eligible for eculizumab, which would rule it out as a comparator, ~~but if any were treated with current ECM then they might.~~ ”	It is unclear what the end of the sentence refers to, as text seems to be missing. Therefore, this part should be deleted or rephrased.	Deleted.
Page 29, Section 2.5 “The company did not perform any subgroup analyses.”	“The company presented subgroup data for clinical outcomes, but did not perform any subgroup analyses in the economic model. ”	Subgroup analyses for the primary endpoint of the APPEAR-C3G trial were presented in Section 2.4.3.1 of the CS (page 51–52). Analyses of the native kidney and post-transplant recurrent cohorts of the Phase 2 trial were presented in Section 2.5.1.4 and Section 2.5.2.2 (extension study data) of the CS. The rationale for not performing subgroup analyses in the economic model is summarised in Section 2.7 (page 77–78) and	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		Section 3.11 (page 139) of the CS.	
Page 57, Section 3.2.5 "The EAG is also concerned that there was no relevant subgroup analysis conducted on patients with C3G recurrence post-transplant, with the limited data provided by the single arm Phase 2 trial, and we are of the position an ITC could have been performed to generate data relevant to this subpopulation."	~~"The EAG is also concerned that there was no relevant subgroup analysis conducted on patients with C3G recurrence post-transplant, with the limited data provided by the single arm Phase 2 trial, and we are of the position an ITC could have been performed to generate data relevant to this subpopulation."~~	Relevant data from the cohort with post-transplant recurrence are presented in Section 2.5.1.4 and Section 2.5.2.2 of the CS; Novartis would therefore suggest removing this note.	Amended.

Key Issue 4: "Suboptimal approach of estimating eGFR slopes"

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Section 1.5, Table 1.5 "The EAG requested analyses: 1) use RaDaR data to inform SoC and apply the iptacopan treatment effect based on the randomised comparison from APPEAR-C3G to inform the iptacopan; and 2) use pre-iptacopan data from APPEAR-C3G to inform SoC and apply the iptacopan treatment effect based on the randomised comparison from APPEAR-C3G to inform the iptacopan."	"The EAG requested analyses: 1) use RaDaR data to inform SoC and apply the iptacopan treatment effect based on the randomised comparison from APPEAR-C3G to inform the iptacopan; and 2) use pre-iptacopan data from APPEAR-C3G to inform SoC and apply the iptacopan treatment effect based on the randomised comparison from APPEAR-C3G to inform the iptacopan.	Clinical experts consulted by Novartis had concerns regarding the clinical validity of both of the requested analyses, which should be reflected in the EAG report. For option 1, the clinicians expressed concerns regarding combining data from two different sources and differences in the included populations.¹ While APPEAR-C3G enrolled patients with UPCR ≥ 1 g/g, the RaDaR eGFR slope was generated based on all C3G patients	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	The company provided these analyses, while highlighting clinicians' concerns regarding combining data from different sources and populations; therefore, results should be interpreted with caution."	in the registry, including patients who had milder disease (UPCR <1 g/g). Given that high UPCR indicates an increased risk of rapid eGFR decline, this difference in populations represents an important limitation of the requested scenario analysis,¹ and results should be interpreted with caution (see CQ response B7 c)). Similarly for option 2, the clinicians consulted by Novartis considered the iptacopan eGFR slope used in this scenario analysis implausible and not supported by the available trial data¹ (see CQ response B7 d) for further details). The context of these analyses is therefore important to note as part of the EAG report, for a balanced presentation of the information provided to date.	
Page 90, Section 4.2.6.1 "2) Single arm (iptacopan) before-after comparison using APPEAR-C3G including the open-label extension study (CS base-case). 3) Single arm (iptacopan) before-after comparison using APPEAR-C3G including the open-label extension study	"2) ~~Single arm (iptacopan)~~ before-after comparison using APPEAR-C3G including the open-label extension study (CS base-case). 3) ~~Single arm (iptacopan)~~ before-after comparison using APPEAR-C3G ~~including the open-label extension study~~ and Phase 2 native kidney cohort A	Rephrasing for clarity. "Single-arm" suggests that only data from the iptacopan arm were used, however, these analyses used data from the full trial population (both arms) for generation of pre- and on-iptacopan eGFR slopes.	Amended as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
and Phase 2 native kidney cohort A (CS scenario analysis). The company selected the single arm (iptacopan) before-after comparison...	including the open-label extension study (CS scenario analysis). The company selected the ~~single arm~~ (iptacopan) before-after comparison...	In option 3), open-label extension study data was also included for patients who had originated from the Phase 2 study.	
Page 90-91, Section 4.2.6.1, Table 4.4 <i>“Single arm (iptacopan) before-after comparison using APPEAR-C3G including the open-label extension study (CS base-case)”</i> <i>“Single arm (iptacopan) before-after comparison using APPEAR-C3G including the open-label extension study and phase 2 native kidney cohort A (CS scenario)”</i>	<i>“~~Single arm (iptacopan) before-after comparison using APPEAR-C3G including the open-label extension study (CS base-case)~~”</i> <i>“~~Single arm (iptacopan) before-after comparison using APPEAR-C3G including the open-label extension study and phase 2 native kidney cohort A~~ including the open-label extension study (CS scenario)”</i>		Amended as proposed.
Page 92, Section 4.2.6.4 “The company, however, considered the SoC eGFR slope based on the randomised double-blind period of APPEAR-C3G to be implausible based on clinical advisors input and inconsistency with published literature, their clinical experience and real-world RaDaR data on the median time from diagnosis to kidney failure.”	“The company, however, considered the SoC eGFR slope based on the randomised double-blind period of APPEAR-C3G to be implausible based on clinical advisors’ input and, which had highlighted the inconsistency with published literature, their clinical experience and real-world RaDaR data on the median time from diagnosis to kidney failure.”	Rephrasing for clarity.	Not a factual inaccuracy.
Page 92, Section 4.2.6.4	“This approach preserves randomisation for the estimated treatment effect and uses the SoC eGFR slope based on	The EAG’s current statement that this approach is, “according to the company”, “consistent with clinical	Amended by removing “that is (according to the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“This approach preserves randomisation for the estimated treatment effect and uses the SoC eGFR slope based on real-world RaDaR data that is (according to the company) consistent with clinical advisors input and published literature.”	real-world RaDaR data that is ~~(according to the company) consistent with clinical advisors input and published literature~~; however, the company’s clinical advisors cautioned against the use of this scenario due to differences in the populations of APPEAR-C3G (UPCR ≥ 1 g/g) and RaDaR (any UPCR level).”	advisors input and published literature” is a factually inaccurate summary of the input which Novartis received from clinical advisors. As explained in the response to CQ B7 c), the consulted clinicians expressed concerns regarding combining data from two different sources and differences in the included populations.¹ While APPEAR-C3G enrolled patients with UPCR ≥ 1 g/g, the RaDaR eGFR slope was generated based on all C3G patients in the registry, including patients who had milder disease (UPCR < 1 g/g). Given that high UPCR indicates an increased risk of rapid eGFR decline, clinicians highlighted that for the subgroup of patients reflecting the APPEAR-C3G inclusion criteria (UPCR ≥ 1 g/g), they would expect a steeper eGFR slope with SoC than informed by the RaDaR analysis in all C3G patients.¹ Therefore, it is not accurate to say that the company believes this approach is consistent with “clinical advisors’ input”.	<i>company) consistent with clinical advisors input and published literature”.</i>
Page 114, Section 6.4 “The EAG concluded that the approach of estimating the eGFR slope for SoC based on RaDaR (data that is, according to the company, consistent with clinical advisors input and published literature) and subsequently applying the iptacopan treatment effect from the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope to be the most reasonable for (relative) treatment effectiveness in the economic model.”	“The EAG concluded that the approach of estimating the eGFR slope for SoC based on RaDaR ~~(data that is, according to the company, consistent with clinical advisors input and published literature)~~ and subsequently applying the iptacopan treatment effect from the randomised double-blind period of APPEAR-C3G to inform the iptacopan eGFR slope to be the most reasonable for (relative) treatment effectiveness in the economic model; however, the company’s clinical advisors cautioned against the use of this scenario due to differences in the populations of APPEAR-C3G (UPCR ≥ 1 g/g) and RaDaR (any UPCR level).”	Amended by removing “(data that is, according to the company, consistent with clinical advisors input and published literature)”.	Amended by removing “(data that is, according to the company, consistent with clinical advisors input and published literature)”.
Page 114, Section 6.4	“Using a before-after comparison (i.e., pre-iptacopan data for SoC and on-iptacopan data for iptacopan) based on	The EAG has not justified how it arrived at a conclusion that this approach results in a likely bias. Other	Amended by changing “likely

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“Using a before-after comparison (i.e., pre-iptacopan data for SoC and on-iptacopan data for iptacopan) based on APPEAR-C3G and the open-label extension study rather than using the randomised double-blind period of APPEAR-C3G likely biased the estimated eGFR slopes.”	APPEAR-C3G and the open-label extension study rather than using the randomised double-blind period of APPEAR-C3G ~~likely biased the estimated eGFR slopes~~ is considered suboptimal by the EAG, as the resulting iptacopan treatment effect was based on an observational comparison rather than a randomised comparison and is therefore prone to bias.	sections of the EAG report (page 15 and page 92) use more balanced wording, which should also be adopted for its conclusion in Section 6.4.	<i>biased</i> ” to “ <i>is prone to biasing</i> ”.

Key Issue 5: “Assumption of a constant, CKD-stage independent speed of progression”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Section 1.5, Table 1.6 “The above-mentioned analyses requested by the EAG were not implemented by the company in their economic model.”	“The above-mentioned analyses requested by the EAG were not implemented by the company in their economic model, due to a lack of suitable data and advice from clinical experts that an assumption of a linear slope was reasonable. ”	The current wording is inaccurate since it omits the company's attempts to provide the requested analyses and explanations why no changes were implemented in the model. All feasible analyses were provided to the EAG in response to CQ B7 f). However, these were not considered suitable for use in the economic model – which the EAG agrees with on page 92 of the EAG report. Further analyses were not feasible due to very small patient numbers in higher CKD stages, as evidenced by analyses conducted in the response to CQ B7 g). In	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		addition, multiple clinical experts consulted by the company considered it reasonable to assume a constant eGFR decline (see CQ B7 e)).	
Page 15, Section 1.5, Table 1.6 “Analyses using CKD stage-dependent and time-dependent eGFR decline rates as requested above, potentially informed by other literature/external data if not deemed feasible based on APPEAR-C3G.”	“Analyses using CKD stage-dependent and time-dependent eGFR decline rates as requested above, potentially informed by other literature/external data if ~~not deemed feasible based on APPEAR-C3G.~~ ”	Feasibility of the requested analyses based on APPEAR-C3G has already been assessed and confirmed not to be feasible as outlined in response to CQ B7 f). Current wording which suggests that feasibility is yet to be established should be removed.	Not a factual inaccuracy.
Page 109, Section 6.1.3, Table 6.1 As above	As above		Not a factual inaccuracy.
Page 67, Section 3.2.6.2.3 “These results showed that there were variations in the slope change in the iptacopan treatment arm between double-blind treatment period and open-label treatment.”	“These results showed that there were variations in the slope change in the iptacopan treatment arm between double-blind treatment period and open-label treatment, though these variations should be interpreted with caution, as UK clinicians advised that time frames of 6 months may be too short to robustly estimate changes in eGFR. ”	The EAG’s summary omits that eGFR slopes for the double-blind and open-label periods were based on only 6 months of data each, a time frame which UK clinicians considered may be too short to robustly estimate changes in eGFR. ² eGFR slope analyses based on longer follow-up were considered more robust and meaningful by clinical advisors, ^{1, 2} (see CQ response A7). This information is important to add for a factual, balanced presentation of the data.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 92, Section 4.2.6.4 “Additionally, time-dependent eGFR decline rates were provided in Table 5 of the clarification response, indicating that eGFR slopes varied over time over the pre-randomisation, double-blind and open-label treatment periods.”	“Additionally, time-dependent eGFR decline rates were provided in Table 5 of the clarification response, indicating that eGFR slopes in the iptacopan arm varied ~~over time over the pre-randomisation~~, between the double-blind and open-label treatment periods, though these variations should be interpreted with caution, as UK clinicians advised that time frames of 6 months may be too short to robustly estimate changes in eGFR.”	Please see the row above. In addition, the current text fails to consider that the pre-randomisation and placebo data reflect eGFR slope on current SoC, which are expected to change once patients initiate iptacopan. Therefore, the sentence should be rephrased as suggested.	Not a factual inaccuracy.

Key Issue 6: “Assumption of a constant treatment discontinuation rate for patients on iptacopan who have not reached kidney failure”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Section 1.5, Table 1.7 “The company should provide full details of the TTD model selection process based on the NICE DSU TSD 14 guidance for the EAG to assess the most appropriate curve to inform treatment discontinuation in the economic model.”	Novartis suggests that this statement is deleted, or otherwise further clarified.	In response to CQ B8, Novartis provided parametric survival analysis in line with NICE DSU TSD 14 guidance, including all standard extrapolations and AIC/BIC statistical fit rankings based on APPEAR-C3G and pooled trial data (also see section “B8 - Parametric survival analysis” of the document	Not a factual inaccuracy. The company's assessment was mainly focussed on statistical fit (i.e. AIC/BIC), while details on other TSD 14 criteria (e.g. visual inspection, clinical validity and external data) were missing.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93, Section 4.2.6.4 “The EAG noted, however, that the company did not provide further details on these clinical expert inputs, and that various other criteria from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance to assess the most suitable parametric model were lacking (e.g. evidence to assess the clinical plausibility of the long-term TTD estimates resulting from the parametric survival curves). [..] However, the company should provide full details of the TTD model selection process based on the NICE DSU TSD 14 guidance for the EAG to assess the most appropriate curve to inform treatment discontinuation in the economic model.”	Novartis suggests that this statement is deleted, or otherwise further clarified.	titled ‘Novartis DoF_2025_Clarification questions supplementary analyses’ in the reference pack of the CQ response). All standard parametric survival functions are further included in the provided economic model, allowing the EAG to test any other preferred assumptions. Therefore, the company is unclear as to what information is lacking and this sentence should be deleted, or otherwise further clarified by the EAG.	As above.
Page 109, Section 6.1.3, Table 6.1, column ‘Required additional evidence or analyses’ “Full details of the TTD model selection process based on the NICE DSU TSD 14 guidance.”	Novartis suggests that this statement is deleted, or otherwise further clarified.		As above.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 114, Section 6.4 “Although the log-normal curve was selected based on the currently available evidence, a more detailed explanation of the TTD model selection process, as per NICE DSU TSD 14 guidance, is necessary for a comprehensive assessment.”	Novartis suggests that this statement is deleted, or otherwise further clarified.		As above
Page 93, Section 4.2.6.4 “... the EAG adopted the log-normal curve based on the APPEAR-C3G population only (in line with the iptacopan treatment effect in the EAG base-case) to inform treatment discontinuation in its base-case.”	~~“... the EAG adopted the log-normal curve based on the APPEAR-C3G population only (in line with the iptacopan treatment effect in the EAG base-case) to inform treatment discontinuation in its base-case.”~~	The EAG base case, as detailed in Section 6 of the EAG report and implemented in the economic model version shared by the EAG, does not include the log-normal curve to inform treatment discontinuation. Therefore, these text elements should be removed, or otherwise the EAG’s base case requires amendment.	Amended by removing “As a constant treatment discontinuation rate was considered questionable, also confirmed by the EAG’s clinical expert stating that it is unclear how much the discontinuation rate will grow over subsequent years, the EAG adopted the log-normal curve based on the APPEAR-C3G population only (in line with the iptacopan treatment effect in the EAG base-case) to inform treatment discontinuation in its base-case”.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 114, Section 6.4 “Although the log-normal curve was selected based on the currently available evidence, ...”	~~“Although the log-normal curve was selected based on the currently available evidence, ...”~~		Amended as proposed.

Key Issue 7: “Assumption of a constant iptacopan treatment effect over the model time horizon while patients remained on treatment”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Section 1.5, Table 1.8 “The analyses requested by the EAG were not implemented by the company in their economic model.”	“The analyses requested by the EAG were not feasible due to data limitations, and treatment effect waning was not implemented by the company in their economic model based on clinical expert opinion indicating this was not appropriate. ”	The specific analyses requested by the EAG in CQ B9 b), i.e. time-to-event data on CKD progression for iptacopan + SoC versus SoC alone, were not feasible since a limited number of CKD stage transitions were observed during APPEAR-C3G, and the number of participants in later CKD stages at baseline was very small (placebo arm: ■ patients each in CKD stages 3a and 3b, ■ patients in CKD stage 4; iptacopan arm: ■ patients in CKD stage 3a, ■ patients in CKD stage 3b, ■ patients in CKD stage 4; see section B7 g) of the document titled ‘Novartis DoF_2025_Clarification questions supplementary analyses’ in the reference pack of the CQ response). An analysis of CKD stage transition probabilities conducted on the same data for CQ B7 g) did not	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		yield meaningful results, which the EAG agrees with on page 94 of the EAG report (first paragraph). As explained in the response to CQ B9 b), the same limitations would apply to time-to-event analyses conducted on the same set of data and therefore, the requested analyses were not considered feasible. This should be captured in the description of the key issue, for a balanced presentation of the information provided to date. In addition, justification for not including treatment effect waning was provided in response to CQ B9 a), based on the mode of action, clinical trial data, and input from clinical advisors who considered it inappropriate to incorporate non-evidence-based waning assumptions into the economic model.¹	
Page 93, Section 4.2.6.4 “However, the company did not provide the evidence requested by the EAG in clarification question	“However, the company did not provide the evidence requested by the EAG in clarification question B9b to assess potential treatment waning (time-to-event data on CKD progression), stating that this was not deemed feasible due to the limited number of CKD stage transitions were observed during APPEAR-C3G.”	To be specific about the analyses that Novartis deemed not feasible and provide additional clarity for readers what the explanation relates to, we suggest adding additional text as proposed.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
B9b to assess potential treatment waning, stating that this was not deemed feasible due to the limited number of CKD stage transitions were observed during APPEAR-C3G."			
Page 109, Section 6.1.3, Table 6.1, row 'Assumption of a constant iptacopan treatment effect over the model time horizon while	This text should be deleted.	This was requested by the EAG in CQ B9, and the rationale for the requested analyses being infeasible as well as further justification for not assuming treatment effect waning were provided by Novartis in its response (see above).	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients remained on treatment' Columns 'Alternative approaches' and 'Required additional evidence or analyses': "Further justification and analyses to assess the assumption of a constant treatment effect during the observed period."			

Key Issue 8: “(Face) validity of the chosen CKD stage 5+ utilities” and other utility inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17, Section 1.5, Table 1.9 “It further requested a more detailed overview of relevant TAs to cross-validate utilities.”	“It further requested a more detailed overview of relevant TAs to cross-validate utilities, which was provided by the company as a comprehensive TLR of 13 previous TAs. ”	A detailed overview and discussion of utilities used in previous TAs had already been provided in the CS, Section 3.4.3 and Appendix F, as well as subsequently in response to CQ B13. The EAG’s summary should not omit the information provided by the company.	Not a factual inaccuracy.
Page 110, Section 6.1.3, Table 6.1 “A more detailed overview of relevant TAs to cross-validate utilities.”	“A more detailed overview of relevant TAs to cross-validate utilities, which was provided by the company as a comprehensive TLR of 13 previous TAs. ”		Not a factual inaccuracy.
Page 95, Section 4.2.8.1 “Additionally, NICE TAs on general CKD published in the last 10 years were reviewed and 13 studies identified. (Table 42).”	“Additionally, NICE TAs on general CKD published in the last 10 years were reviewed and 13 TAs identified. (Table 42).”	NICE TAs, not studies, were identified and reviewed.	Amended as proposed.
Page 17, Section 1.5, Table 1.9 “Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients might help to resolve this key issue.”	“Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients might help to resolve this key issue, however, such data are not available from APPEAR-C3G. ”	Novartis acknowledges that these data would be of relevance to the model, however there were no patients in CKD stage 5 within APPEAR-C3G and therefore these data are not available (see CS Section 3.4.1, Table 40).	Not a factual inaccuracy.
Page 110, Section 6.1.3, Table 6.1 “Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients.”	“Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients, however, such data are not available from APPEAR-C3G. ”		Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 114, Section 6.4 “Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients might help to resolve this key issue.”	“Analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients might help to resolve this key issue, however, such data are not available from APPEAR-C3G. ”		Not a factual inaccuracy.
Page 96, Section 4.2.8.3 “The clinical advisor consulted by the company deemed the post-transplant HS utility (0.76) “relatively low” and supported alternatively the use of Liem 2008 value (0.81).”	“The clinical advisor consulted by the company deemed the post-transplant HS utility (0.76) “relatively low” and supported alternatively the use of Liem 2008 value (0.81); however, they also highlighted expected variation in HRQoL between patients, since not all patients have good outcomes following a transplant, for example, some patients experience surgical complications. ”	Part of the clinical advisor’s input was missing (as detailed in CQ response B13 a)), and this is necessary to include to correctly represent their input. ³	Not a factual inaccuracy.
Page 96, Section 4.2.8.3 “In response to clarification question B13, the company stressed the considerable impact of KRT on HRQoL, the use of Lee 2005 utility values in prior TAs (Table 34) and shortcomings related to the Liem 2008 meta-analysis. However, the Liem 2008 was also considered appropriate in prior TAs (Table 34)”	“In response to clarification question B13, the company stressed the considerable impact of KRT on HRQoL, the use of Lee 2005 utility values in seven prior TAs (Table 34) and shortcomings related to the Liem 2008 meta-analysis. However, the Liem 2008 was also considered appropriate in two prior TAs (Table 34)”	For full transparency regarding the extent that Lee 2005 and Liem 2008, respectively, were used in previous TAs to inform the NICE committee’s decision-making, the number of appraisals should be added for each source (see CS Table 42).	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 96, Section 4.2.8.2, Table 4.5, Column “Justification” “UK clinical and health economic expert opinion.”	Row 2–6 (CKD stage 1–4), please change the justification column to “Regarded most suitable by UK clinical and health economic experts” Row 7 (CKD stage 5), please change the justification column to “Utility values for CKD stage 5 were not available from APPEAR-C3G. Jesky 2016, a UK study, was used in two previous NICE appraisals and considered appropriate by UK clinical and health economic experts” Row 8–10 (Dialysis and Post-transplant), please change the justification to “KRT utility values were not available from APPEAR-C3G. Lee 2005, a UK study, was used in 7 previous NICE appraisals and considered most appropriate by UK clinical and health economic experts.”	Since Table 4.5 of the EAG report references the CS, the company requests that complete justification for the used health state utilities is included, as reflected in Section 3.4.4.1 of the CS (reiterated in response to CQ B12 and B13).	Not a factual inaccuracy.
Page 97, Section 4.2.8.3 “From older and different CKD populations, TAs presented by the company in clarification response, Table 33 had mostly lower utilities compared to the CS.”	~~“From older and different CKD populations, TAs presented by the company in clarification response, Table 33 had mostly lower utilities compared to the CS.”~~	The economic model applies age adjustments for utility values, as detailed in CS Section 3.4.4.1. As visible from Table 43 in the CS, in the case of Jesky 2016 (scenario analysis) these age adjustments led to utilities which were initially lower than APPEAR-C3G utilities to become higher than APPEAR-C3G utilities. Therefore, unless the EAG has assessed all utilities	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		following age adjustments, the statement might be inaccurate and should be deleted.	
Page 97, Section 4.2.8.3 “The Adelphi DSP C3G study (N=100), which included 32 UK patients, reported EQ-5D-5L over a 9-month period.”	“The Adelphi DSP C3G study (~~N=100~~), ~~which included 32 UK patients~~ , reported EQ-5D-5L based on 100 observations over a 9-month period. ”	The Adelphi DSP study overall reported on 385 patients, 100 of which completed the EQ-5D. No information is provided in the published source on how many UK patients completed the EQ-5D. Additionally, patients did not report EQ-5D over a 9-month period (with multiple measurements), but the Adelphi DSP study was conducted as a cross-sectional survey which was open for 9 months.	Amended.
Page 113, Section 6.2, Table 6.3 “Scenario Analysis (7 - HD and PD KRT utilities based on Liem 2008)”	Scenario Analysis (7 - ~~HD and PD dialysis~~ and post-transplant KRT utilities based on Liem 2008)	The EAG report is inconsistent with regards to whether their Scenario Analysis 7 includes Liem 2008 utilities only for dialysis, or for dialysis and post-transplant health states. The suggested correction reflects how the scenario has been implemented in the EAG’s model.	Amended as proposed.
Page 95, Section 4.2.8.1 “It was discarded in the CS because CKD stage 1 showed a lower utility than CKD stage 4/5.”	“It was discarded in the CS because CKD stage 1 ~~showed a lower utility than CKD stage 4/5~~ patients had the worst HRQoL after patients with CKD stage 4/5. ”	The statement is inaccurate. CKD stage 1 patients had the worst HRQoL after patients with CKD stage 4/5, but the CKD stage 1 utility was not lower than the CKD stage 4/5 utility (utility values for CKD stage 1: 0.67; CKD stage 2: 0.77; CKD stage 3a: 0.80; CKD stage 3b: 0.70; CKD stage 4/5: 0.58) (CS page 110).	Amended as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 97, Section 4.2.8.3 “The study also showed unexpectedly increasing values for CKD stages 1-3A. (Table 30).”	“The study also showed unexpectedly increasing values for CKD stages 1-3A, with implausibilities potentially owing to the small sample size. (Table 30)”	It is not unexpected that the small sample size of Adelphi DSP would result in uncertainties in the derived utilities, which should be recognised. Utilities generated from APPEAR-C3G were based on a substantially larger sample size (e.g. CKD stage 1: APPEAR-C3G n=286, Adelphi DSP n=16).	Not a factual inaccuracy.
Page 97, Section 4.2.3.8 “The EAG is concerned about the considerable uncertainty surrounding early CKD stage utilities, and therefore requested a scenario analysis using the Adelphi DSP study which the company did not provide.”	Option 1: “The EAG is concerned about the considerable uncertainty surrounding early CKD stage utilities, and therefore requested a scenario analysis using the Adelphi DSP study ~~which the company did not provide,~~ however, the company did not consider that the study reported suitable data.” Option 2: “The EAG is concerned about the considerable uncertainty surrounding early CKD stage utilities, ~~and therefore requested a scenario analysis using the Adelphi DSP study which the company did not provide.~~”	The statement that “the company did not provide [the requested analysis]” is a factually inaccurate representation of Novartis’ response to the request. In its response to CQ B13 c), Novartis explained that Lafayette 2024 (congress abstract) and Sinha 2025 (submitted manuscript) both report on the same Adelphi DSP study. The congress abstract reports implausible utility values (see above and B13 b)) while the submitted manuscript only reports EQ-5D utility values for eGFR <30 mL/min/1.73m² and >30 mL/min/1.73m², but not by CKD stage. In addition, the limitation that a US tariff was used remains. Therefore, the submitted manuscript was not considered to provide suitable data for cross-validation of utility values or a scenario analysis.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 98, Section 4.2.3.8 “The EAG requested the company in clarification question B14 to verify the chosen disutility value of 0.156 with additional literature, which the company did not provide. As impact is expected to be small, the EAG regards the uncertainty of this estimate a minor limitation.”	“The EAG requested the company in clarification question B14 to verify the chosen disutility value of 0.156 with additional literature in a UK setting, which the company did not provide as the source for the disutility (Oppong 2013) collected data in England and generated utility values using a UK tariff and was therefore considered a suitable study. As impact is expected to be small, the EAG regards the uncertainty of this estimate a minor limitation. However, the company conducted two scenario analyses using disutility values of 0.1 and 0.2, respectively, which demonstrated that the impact on the ICER is negligible.”	The company provided justification for the chosen disutility value and literature in response to CQ B14. The current text further omits that the company presented two scenario analyses which resolve uncertainty as to the impact being minor (see B14 c); impact on ICER [REDACTED] % to [REDACTED] %).	Not a factual inaccuracy.

Key Issue 9: “Majority of QALYs and costs accumulated beyond the observed data”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17, Section 1.5, Table 1.10 “The majority of absolute and incremental QALYs and costs for iptacopan + SoC and SoC were accumulated beyond the observed data period. Moreover, the proportion of costs accumulated beyond the observed	“The majority of absolute and incremental QALYs and costs for iptacopan + SoC and SoC were accumulated beyond the observed data period, however given the lifetime horizon and the baseline age of 27.9, this is expected. As similarly expected, due to iptacopan slowing time to KRT and KRT being a major cost	C3G is a disease that affects young people. With the model using a lifetime horizon, it is therefore expected that costs/QALYs would accumulate outside of the period of observed data.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
data for SoC was substantially larger than for iptacopan + SoC.”	driver, Moreover, the proportion of costs accumulated beyond the observed data for SoC was substantially larger than for iptacopan + SoC (in which iptacopan acquisition costs are accrued pre-KRT). ”	Since explanations on the mechanisms behind how the model accrues costs and QALYs have already been provided in CS Appendix H, as well as the response to CQ B19, Novartis suggests adding these additional details for clarity.	
Page 17, Section 1.5, Table 1.10 “Additional explanation as to the mechanism by which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence.”	Given that the requested explanation has already been provided, the statement should be deleted.	Explanations as to how the model generates differences in QALYs and costs were provided in CS Appendix H, as well as the response to CQ B19 (please see summarised in above row, proposed amendments). Therefore, this statement should be removed.	Not a factual inaccuracy.
Page 104, Section 5.1 “Furthermore, the EAG noted that the majority of incremental QALYs and costs are also accumulated beyond the observed period.”	“Furthermore, the EAG noted that the majority of incremental QALYs and costs are also accumulated beyond the observed period, however given the lifetime horizon and the baseline age of 27.9, this is expected. ”	Novartis suggests adding this information for clarity.	Not a factual inaccuracy.
Page 104, Section 5.1 “Given the uncertainty regarding the long-term extrapolation of treatment effect (EAG report Section 4.2.6), the EAG would like to see explanation as to the mechanism by	“Given the uncertainty regarding the long-term extrapolation of treatment effect (EAG report Section 4.2.6), the EAG would like to see explanation as to the mechanism by	This information was provided by Novartis in the CS Appendix H, as well as the response to CQ B19, which should be reflected for factual accuracy.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence.”	which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence; this was requested and provided by the company. ”		
Page 110, Section 6.1.3, Table 6.1, row ‘Majority of QALYs and costs accumulated beyond the observed data’, column ‘Source of uncertainty’: ”Transparency”	Column ‘Source of uncertainty’: “ ~~Transparency~~ Methods ”	It is unclear how the EAG’s concerns relate to transparency. The model is transparent as to how these results are generated and as noted above, explanations were provided in the CS Appendix H as well as the response to CQ B19. Therefore, this item should be reclassified.	Not a factual inaccuracy.
Page 114, Section 6.4 “Fourthly, the EAG noted that the majority of absolute and incremental QALYs and costs for iptacopan + SoC and SoC were accumulated beyond the observed data period, requiring explanation as to the mechanism by which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence.”	“Fourthly, the EAG noted that the majority of absolute and incremental QALYs and costs for iptacopan + SoC and SoC were accumulated beyond the observed data period, requiring explanation as to the mechanism by which the model generated these differences and justification as to why these generated differences are plausible provided the available evidence; this was requested and provided by the company. ”	This information was provided by Novartis in the CS Appendix H, as well as the response to CQ B19, which should be reflected for factual accuracy.	Not a factual inaccuracy.

Key Issue 10: “Lack of transparency regarding expert consultation”

Description of problem		Description of proposed amendment	Justification for amendment	EAG response
Page 17–18, Table 11.1		Novartis asks that this key issue is removed.	The EAG report gives the impression that separate “full minutes” of advisory board meetings and consultations exist, which Novartis refuses to share with the EAG. This is incorrect. As explained in the response to CQ B23, the reports included in the CS reference pack represent the only written records of the discussions held; no separate minutes were produced. For additional clarity, Novartis wishes to explain that all expert consultations were recorded, with reports being written based off the recordings. Any partial notes which may have been taken by individual meeting participants were not consolidated, verified or archived by Novartis; therefore, other than the provided meeting reports, no full written records exist. Verification of the meeting report for accuracy and completeness was done against the recording. As per the contracts between Novartis and the advisors, recordings were created for purposes of the meeting write-up only and deleted following finalisation of the report. Contracts between Novartis and advisors permit sharing of the meeting report as part of Novartis HTA submissions to NICE. Novartis would like to further highlight that the submitted reports provide comprehensive detail	Not a factual inaccuracy.
Report Section	5.3			
Description of issue and why the EAG has identified it as important	Various modelling assumptions in the CS were justified based on expert opinion from advisory board meetings and consultations. The EAG had no access to the full minutes of these advisory board meetings.			
What alternative approach has the EAG suggested?	The EAG requested access to the full meeting minutes in clarification question B23, but did not receive these.			
What is the expected effect on the cost effectiveness estimates?	Unclear.			
What additional evidence or analyses might help to	Provide the full advisory board meeting minutes.			

Description of problem		Description of proposed amendment	Justification for amendment	EAG response
resolve this key issue?			regarding the expert consultations that took place, including information on the advisors who participated, the full agenda (where a formal agenda existed), a summary of the information presented to advisors, and a full representation of the discussions held and advisors' conclusions. Overall, four detailed reports were provided to the EAG within the CS and CQ response reference packs: • Novartis. Data on File: Virtual Advisory Board: C3 Glomerulopathy (C3G): Exploring the Current Clinical Landscape, 2022. – 24 pages • Novartis. Data on File: Advisory Board Report - Clinical Interpretation of Data for Iptacopan in C3G, 2024. – 32 pages • Novartis. Data on File: Clinical and Model Validation for Iptacopan in C3G, 2025. – 23 pages • Novartis. Data on File: Clinical expert input for Novartis' response to iptacopan C3G EAG clarification questions, 2025. – 19 pages As all available information on expert consultations has already been provided to the EAG, this key	
CS = company submission; EAG = External Assessment Group				

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		issue and all other references to a “lack of transparency” in relation to expert consultations held by Novartis should be removed.	
Page 93, Section 4.2.6.4 “The EAG noted, however, that the company did not provide further details on these clinical expert inputs, and that various other criteria from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance to assess the most suitable parametric model were lacking (e.g. evidence to assess the clinical plausibility of the long-term TTD estimates resulting from the parametric survival curves).”	Novartis asks that this statement is removed.	As noted above, all information regarding clinical expert inputs was included within the reports provided. (Please note the comments regarding the reference to TSD 14 with Key issue 6.)	Not a factual inaccuracy.
Page 105, Section 5.3.5 “... a) no access to minutes of advisory board meetings, ... a) Various modelling assumptions in the CS were justified based on expert opinion from advisory board meetings and consultations. The EAG noted however, that only summaries rather than full meeting minutes of these were provided, although requested in clarification question B23. The EAG considers this to be a serious transparency issue as it is unable to verify various assumptions made by the company, and the full meeting details should therefore be provided.”	Novartis asks that this statement is removed.	Full meeting reports from expert consultations were provided; see above.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 114, Section 6.4 “Finally, the company did not provide the full advisory board report, which was considered a serious transparency issue as it hinders validation of various modelling assumptions informed by clinical experts.”	Novartis asks that this statement is removed.		Not a factual inaccuracy.
Page 110, Section 6.1.3, Table 6.1 <i>Row:</i> Lack of transparency regarding expert consultation	Novartis asks that this row is removed.		Not a factual inaccuracy.

Section 2: Other factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG concluding remarks			
Page 18, Section 1.6 “In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of iptacopan + SoC, which can be partly resolved by the company. This includes providing CKD stage-dependent and time-dependent eGFR decline rates, full details of the	“In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of iptacopan + SoC, ~~which can be partly resolved by the company. This includes providing CKD stage-dependent and time-dependent eGFR decline rates, full details of the time to treatment discontinuation (TTD) model selection process based on the NICE Decision Support Unit (DSU)~~ Technical Support Document (TSD) 14	As noted in Section 1, Novartis has either already provided this information in the CS or CQ response or alternatively provided rationale why it was not feasible to provide the requested information; therefore, the remaining uncertainty is unlikely to be resolvable by the company. While Novartis agrees that there is uncertainty in the ICERs, it disagrees	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
time to treatment discontinuation (TTD) model selection process based on the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance, analyses to assess the assumption of a constant treatment effect during and beyond the observed period, analyses of additional (patient-level) European Quality of Life-5 Dimensions (EQ-5D) data on CKD stage 5+ patients, explanation and justification of the mechanisms by which the economic model generated a substantial proportion of QALYs and costs beyond the observed data, and providing the full advisory board meeting minutes. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of iptacopan + SoC compared with SoC."	guidance, analyses to assess the assumption of a constant treatment effect during and beyond the observed period, analyses of additional (patient-level) European Quality of Life-5 Dimensions (EQ-5D) data on CKD stage 5+ patients, explanation and justification of the mechanisms by which the economic model generated a substantial proportion of QALYs and costs beyond the observed data, and providing the full advisory board meeting minutes. Therefore, the EAG believes that the CS ~~nor~~ and the EAG report contains an uncertain unbiased ICER of iptacopan + SoC compared with SoC."	that these uncertainties necessarily lead to bias; the methods used to determine the ICER were discussed with multiple clinical experts and following a review of previous CKD appraisals, to provide a consistent and clinically plausible approach.	
Page 115, Section 6.4 "In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of iptacopan + SoC,	"In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of iptacopan + SoC, ~~which can be partly resolved by the company. This includes providing CKD stage dependent and time dependent~~		Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
which can be partly resolved by the company. This includes providing CKD stage-dependent and time-dependent eGFR decline rates, full details of the TTD model selection process based on the NICE DSU TSD 14 guidance, analyses to assess the assumption of a constant treatment effect during and beyond the observed period, analyses of additional (patient-level) EQ-5D data on CKD stage 5+ patients, explanation and justification of the mechanisms by which the economic model generated a substantial proportion of QALYs and costs beyond the observed data, and providing the full advisory board meeting minutes. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of iptacopan + SoC compared with SoC."	eGFR decline rates, full details of the time to treatment discontinuation (TTD) model selection process based on the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance, analyses to assess the assumption of a constant treatment effect during and beyond the observed period, analyses of additional (patient-level) European Quality of Life 5 Dimensions (EQ-5D) data on CKD stage 5+ patients, explanation and justification of the mechanisms by which the economic model generated a substantial proportion of QALYs and costs beyond the observed data, and providing the full advisory board meeting minutes. Therefore, the EAG believes that the CS ~~nor~~ and the EAG report contains an uncertain unbiased ICER of iptacopan + SoC compared with SoC."		
Description of systematic literature reviews (SLRs)			
Page 30, Section 3.1 "The company performed a systematic literature review (SLR)	"The company performed a systematic literature review (SLR) to identify and summarise the available randomised controlled trial (RCT) and other relevant	The SLR was not limited to studies involving iptacopan, so as to ensure the	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
to identify and summarise the available randomised controlled trial (RCT) and other relevant evidence relating to the efficacy and safety of iptacopan for the treatment of adults with C3G.”	evidence relating to the efficacy and safety of iptacopan and other interventions for the treatment of adults with C3G.”	broadest possible evidence base was identified.	
Page 83, Section 4.1.1 “Appendices E and F of the CS provide details of SLRs conducted to identify relevant studies on cost effectiveness, cost/health care resource use and HRQoL in the treatment of C3G. [...] The CS, Appendices E and F and the company’s response to clarification ...”	“Appendices E, F and G of the CS provide details of SLRs conducted to identify relevant studies on cost effectiveness, cost/health care resource use and HRQoL in the treatment of C3G. [...] The CS, Appendices E, F and G and the company’s response to clarification ...”	The cost and healthcare resource utilisation SLR was presented in Appendix G of the CS, which has been missed in the listing.	Amended.
Page 113, Section 6.4 “The CS, Appendices E and F, and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use in C3G.”	“The CS, Appendices E, F and G, and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use in C3G.”		Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 83, Section 4.1.1 “• A single set of searches was undertaken to identify relevant studies on the economic evidence and health care cost/resource use in the treatment of C3G. An additional set of searches was conducted to identify relevant HRQoL data.”	“• ~~A single set of~~ Separate searches ~~was~~ were undertaken to identify relevant studies on the economic evidence, ~~and~~ health care cost/resource use in the treatment of C3G. ~~An additional set of searches was conducted to identify, and~~ relevant HRQoL data.”	Three separate SLRs were conducted, each with its own search terms. Please refer to the search strategies in CS Appendices E, F, and G.	Amended.
Page 83, Section 4.1.1 “The searches for economic evidence and healthcare resource were conducted on 16 September 2020 and updated on 10 October 2024.”	“The searches for economic evidence ~~and healthcare resource~~ were conducted on 16 September 2020 and updated on 10 October 2024. The searches for healthcare resource use were conducted on 11 February 2021 and updated on 10 October 2024. ”	These were two separate SLRs, with different search terms and conducted on different dates.	Amended.
Page 113, Section 6.4 As above	As above		Amended.
Page 83, Section 4.1.1 “• For the economic/healthcare resource use SLR conference searches were conducted on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) presentation database and the Health Technology Assessment	“• For the economic/ ~~healthcare resource~~ ~~use~~ SLR conference searches were conducted on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) presentation database and the Health Technology Assessment International (HTAi) website. The healthcare resource use SLR additionally also searched ERA-EDTA	The healthcare resource use SLR was separate to the economic evaluations SLR and also included searches of these two medical congresses.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
International (HTAi) website. For the HRQoL searches, ISPOR, the ERA-EDTA and ASN conferences were searched. All conference proceedings searches were limited to 2019-2024.”	and ASN conferences. For the HRQoL searches, ISPOR, the ERA-EDTA and ASN conferences were searched. All conference proceedings searches were limited to 2019-2024.”		
Generalisability of trial data			
Page 53, Section 3.2.4 “It is clear from the table above that there were minimal UK based participates involved in this trial with only nine in total. Minor imbalances beyond 5% were present across some characteristics including but not limited to those in the iptacopan group being younger and having more patients with lower eGFR (<60 ml/min/1.73 m ²). However, given the small sample of nine, differences by proportion will obviously be larger and appear more pronounced, when in reality these differences reflect only a few patients. The EAG therefore, does not consider these to be remarkable, however the presentation of data that has so few UK based participants does	~~“It is clear from the table above that there were minimal UK based participates involved in this trial with only nine in total~~ Approximately 12% of trial participants (9 of 74 patients) were UK-based. Minor imbalances beyond 5% were present across some characteristics including but not limited to those in the iptacopan group being younger and having more patients with lower eGFR (<60 ml/min/1.73 m ²). However, given the small sample of nine, differences by proportion will obviously be larger and appear more pronounced, when in reality these differences reflect only a few patients. The EAG therefore, does not consider these to be remarkable.; ~~however the presentation of data that has so few UK based participates does not allow for consideration of meaningful generalisability.”~~	While nine is a relatively low number, C3G is an ultra-rare disease, therefore limiting the overall pool of available patients. There were 74 participants in the global pivotal Phase 3 trial, meaning approximately 12% of trial participants were from the UK, which the company would suggest is not a minimal amount.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
not allow for consideration of meaningful generalisability.”			
Page 57, Section 3.2.5 “... the relevance and generalisability of the trial population to the clinical population of England and Wales is of limited evidence, with some differences in characteristics with the RaDaR cohort, and with minimal involvement of UK based sites (three) and participants (nine).”	“... the relevance and generalisability of the trial population to the clinical population of England and Wales is of limited evidence, with some differences in characteristics with the RaDaR cohort, ~~and with minimal involvement of UK based sites (three) and participants (nine).~~ ”		Not a factual inaccuracy.
Page 55, Section 3.2.4 “Baseline mean UPCR of APPEAR-C3G participants was higher (3.40 g/g) compared to the prevalent RaDaR cohort (1.73 g/g).”	“Baseline mean UPCR of APPEAR-C3G participants was higher (3.40 g/g) compared to the prevalent RaDaR cohort (1.73 g/g). This is expected given that APPEAR-C3G focused on a population at higher risk of disease progression, with baseline UPCR ≥1 g/g despite treatment with a maximally tolerated dose of ACEi/ARB. ”	The missing part of the response to CQ A10 provided by the company should be included, to fully reflect the relevant explanation.	Not a factual inaccuracy.
Page 57, Section 3.2.4 “The EAG did not consider the inclusion of nine patients derived from three sites across the UK as constituting a meaningful representation of ‘several UK	~~“The EAG did not consider the inclusion of nine patients derived from three sites across the UK as constituting a meaningful representation of ‘several UK study sites’ or of a meaningful number of patients to justify supportive of~~	As noted above, UK participants comprised approximately 12% of the clinical trial population, due to C3G being an ultra-rare disease. While the company acknowledges that some uncertainty regarding	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
study sites' or of a meaningful number of patients to justify supportive of generalisability. The EAG also notes that there are differences in characteristics between trial patients and those in RaDaR cohort, and while clinical opinion and advice is important and valid and has suggested the trial populations can be generalised, little evidence was presented to support such a generalisation."	~~generalisability.~~ The EAG also notes that there are differences in characteristics between trial patients and those in RaDaR cohort, and while clinical opinion and advice is important and valid and has suggested the trial populations can be generalised, ~~little evidence was presented to support such a generalisation~~ some uncertainty remains."	generalisability of the trial population remains, the company provided a comparison between the trial and RaDaR populations as evidence for this generalisation as part of the response to CQ A10.	
Page 55, Section 3.2.4 "The company included in their submission a copy of the clinical advisory board report which they cited as support of their defences."	"The company included in their submission a copy of the clinical advisory board report which ~~they cited as support of their defences~~ provides evidence on UK clinical experts' views on generalisability of the trial. "	The generalisability of the trial was discussed as part of a UK advisory board, where clinical experts advised that baseline characteristics were generalisable to clinical practice. The advisory board report was presented in the submission as the available evidence, rather than a "defence" of a company position.	Not a factual inaccuracy.
Adverse events			
Page 76, Section 3.2.7.4 "The company was asked to clarify the details of the one death and clarify any cardiovascular (CV) events reported, given the	"The company was asked to clarify the details of the one death and clarify any cardiovascular (CV) events reported; ~~given the potential link between complement inhibition and thrombosis.~~ "	The EAG was not able to explain the source of the putative link between complement inhibition and thrombosis in the CQ call and has also not referenced this statement in the EAG report. As set out in the response to	Not a factual inaccuracy, but amended to reduce ambiguity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
potential link between complement inhibition and thrombosis.”		CQ A14, thrombosis is a frequent complication in paroxysmal nocturnal haemoglobinuria (PNH),⁴ and was therefore an AE of special interest (AESI) in the iptacopan clinical trial programme for PNH.⁵ The inclusion of thrombosis as an AESI was related to PNH as a disease, rather than a general risk associated with complement inhibition. Thrombosis was not an AESI in the iptacopan clinical trials in C3G, and no AEs of thrombosis were reported in patients receiving iptacopan.⁶ Novartis therefore asks for removal of this unsupported statement.	
Page 77, Section 3.2.7.5 “The company was asked to clarify the nature of these SAEs and the rationale for concluding that they were unrelated to iptacopan, as the CS stated that three patients discontinued iptacopan due to AEs (all in the open-label extension study), with SAEs determined not to be related to iptacopan. The company provided the details regarding the three patients who discontinued iptacopan due to	“The company was asked to clarify the nature of these SAEs and the rationale for concluding that they were unrelated to iptacopan, as the CS stated that three patients discontinued iptacopan due to AEs (all in the open-label extension study), with SAEs determined not to be related to iptacopan. The company responded that the causality of the three SAEs that led to discontinuation of iptacopan was assessed by the investigator, and these were classified as unrelated to iptacopan. The company also provided the details	The quoted response was missing the rationale for concluding these SAEs were not related to iptacopan, suggesting that Novartis had not responded to this part of the query. The information, as reflected in the proposed amendment, was provided alongside the nature of the AEs in the response to CQ A13.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
SAEs in the open-label extension study, “One patient discontinued iptacopan due to an SAE of renal impairment [...]”	regarding the three patients who discontinued iptacopan due to SAEs in the open-label extension study, “One patient discontinued iptacopan due to an SAE of renal impairment [...]”		
Page 94, Section 4.2.7 “The CS detailed that all SAEs were infections and proceeded to standardise them to pneumonia and sepsis in a simplifying assumption.”	“The CS detailed that almost all SAEs suspected to be related to iptacopan were infections with encapsulated bacteria (an AE of special interest for iptacopan) leading to pneumonia or consequences thereof such as sepsis and were considered accordingly in the economic analysis. ”	The current statement is an incorrect summary of the information provided in the CS (Section 3.3.4) and needs to be amended.	Amended as follows: <i>“The CS detailed that almost all SAEs suspected to be related to iptacopan were infections with encapsulated bacteria (an AE of special interest for iptacopan) leading to pneumonia or consequences thereof such as sepsis and thus proceeded to standardise them to pneumonia and sepsis in the economic analysis in a simplifying assumption.”</i>
Page 94, Section 4.2.7 “The EAG considers the company’s definition of AEs relevant to the DP, i.e., SAEs suspected to be related to	~~“The EAG considers the company’s definition of AEs relevant to the DP, i.e., SAEs suspected to be related to iptacopan, to be unsatisfactory. First, it diverges from Common Terminology~~	The NICE Health Technology Evaluations Manual does not specify that AEs need to be defined based on the CTCAE, ⁷ and SAEs are a standard AE category in clinical trials.	Amended as follows: Added: <i>“to which the company highlighted that the iptacopan AEs reflect a patient population</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
iptacopan, to be unsatisfactory. First, it diverges from Common Terminology Criteria for Adverse Events (CTCAE) for AEs. Second, it is unclear how “suspected to be related to iptacopan” was assessed and clinically justified. The definition impeded an inclusion of AEs for the comparators, thereby preventing an assessment of differences in consequences on health outcomes and resource use as stipulated by NICE. The EAG is concerned that safety profiles might differ when the comparator treatments are given respectively when iptacopan is added, which the company declines.”	~~Criteria for Adverse Events (CTCAE) for AEs. It is unclear how “suspected to be related to iptacopan” was assessed and clinically justified. The definition impeded an inclusion of AEs for the comparators, thereby preventing an assessment of differences in consequences on health outcomes and resource use as stipulated by NICE.~~ The EAG is concerned that safety profiles might differ when the comparator treatments are given respectively when iptacopan is added, to which the company highlighted that the iptacopan AEs reflect a patient population where it is added to background SoC, which the company declines.”	Additionally, it was clarified in the response to CQ A13, that SAEs “suspected to be related to iptacopan” were assessed and judged by the Investigator. The rationale for only modelling SAEs <i>suspected to be related to iptacopan</i> followed the decision to use data from the broad safety set, maximising sample size and follow-up duration. Since the broad safety set only reports on iptacopan AEs and does not contain a control arm, it only provided data for modelling AEs for iptacopan (with no AEs modelled for the SoC comparator arm) (see CS Section 3.3.4 and response to CQ B10). Novartis did not provide any comment on the potential for the safety profiles of the comparator treatments to differ when iptacopan is added; therefore, the source of the EAG’s statement that “the company declines [that]” is unclear. Instead, Novartis explained in the response to CQ B14 a) that the trial data already reflect the safety profile of iptacopan while being administered in addition to SoC.	<i>where it is added to background SoC, which the company declines.”</i> Removed: “<i>which the company declines</i>”.
Page 94, Section 4.2.7		The described population is not a subgroup of the APPEAR-C3G	Amended as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“Whereas the modelled CS population was native kidney C3G patients with continued risk of disease progression on a maximally tolerated licensed dose of an ACEi or ARB, i.e., a subgroup of the APPEAR-C3G trial (see EAG report Section 4.2.3), ...”	“Whereas the modelled CS population was native kidney C3G patients with continued risk of disease progression on a maximally tolerated licensed dose of an ACEi or ARB, i.e., ~~a subgroup of the APPEAR-C3G trial~~ in line with the inclusion criteria of APPEAR-C3G (see EAG report Section 4.2.3), ...”	population but rather the full trial population, with “continued risk of disease progression” reflected as the inclusion criterion UPCR ≥ 1 g/g. Please refer to the inclusion/exclusion criteria in CS Table 5, Section 2.4.1.	
UPCR analysis			
Page 87, Section 4.2.2 “In clarification response B2, the company concluded (while acknowledging the exploratory nature and small sample size of the analyses) that greater UPCR reductions with iptacopan may translate into greater eGFR benefit, and even modest reductions (<30%) were associated with meaningful improvements in eGFR slope compared to pre-treatment trajectories.”	“In clarification response B2, the company concluded (while acknowledging the exploratory nature and small sample size of the analyses) that greater UPCR reductions with iptacopan may translate into greater eGFR benefit, ~~and even modest~~ while also lower reductions (<30%) were associated with meaningful improvements in eGFR slope compared to pre-treatment trajectories.”	The text is presented as a summary of the company’s conclusion but uses inaccurate wording. The statement should reflect the actual wording as used in the response to CQ B2.	Amended as proposed.
Modelling of transplant frequency			
Page 87-88, Section 4.2.2	“Scenario analyses that reduced or capped transplant frequency led to lower	An overestimate of cost-effectiveness would suggest a higher ICER, therefore	Amended as follows: Added: “ <i>the ICER of</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“Scenario analyses that reduced or capped transplant frequency led to lower incremental cost-effectiveness ratios (ICERs), suggesting that the base-case may conservatively overestimate iptacopan’s cost effectiveness. The probabilities of graft failure and repeated transplantation were derived from RaDaR data, incorporating cycle-based probabilities and transplant eligibility assumptions.”	incremental cost-effectiveness ratios (ICERs), suggesting that the base-case may conservatively overestimate ~~iptacopan’s cost effectiveness~~ the ICER of iptacopan + SoC compared to SoC . The probabilities of graft failure and ~~repeated~~ transplantation were derived from RaDaR data, incorporating cycle-based probabilities and transplant eligibility assumptions.”	the wording should be adjusted for clarity. The word ‘repeated’ in relation to transplantation inputs should be deleted as this does not accurately reflect the model.	<i>iptacopan + SoC compared to SoC</i> ”. Removed: “ <i>iptacopan’s cost effectiveness</i> ”.
Cost-effectiveness model results			
Page 103-104, Section 5.1 Company cost-effectiveness results reported in section 5	“The company updated its base case with the response to the clarification questions, including iptacopan wastage. Updated company base case results are reported in Section 6.”	While cost-effectiveness results shown in Section 5 of the EAG report are correct in reflecting the initial company submission, it would be important to note that the company base case was updated with the CQ response, as otherwise there are unexplained discrepancies with company base case results subsequently reported in Section 6 of the EAG report.	Not a factual inaccuracy. Amended as follows to reduce ambiguity: <i>“The company updated its base-case following clarification questions to include iptacopan wastage costs at discontinuation. The updated company base-case results are reported in section 6.”</i>
Page 104, Section 5.1	“Time to next stage was provided for each CKD stage for the SoC arm,	As explained in response to CQ B19 c), the iptacopan arm in the model	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Time to next stage was provided for each CKD stage for the SoC arm, however, was not provided for the iptacopan + SoC arm. For comparability with SoC, the EAG would like to also see the time to each CKD stage for the iptacopan + SoC arm."	however, was not provided for the iptacopan + SoC arm. ~~For comparability with SoC, the EAG would like to also see the time to each CKD stage for the iptacopan + SoC arm.~~ with the company explaining that time to next stage for the latter would vary across the model time horizon, due to the changing proportion of patients on iptacopan and patients who discontinued iptacopan.	consists of patients on iptacopan and patients who have discontinued iptacopan and switched to SoC alone, with proportions varying over the model time horizon. Therefore, time to next state cannot be easily calculated, as it differs for each model cycle. This explanation has to be included for a factually accurate representation of the company's response.	
Model validation			
Page 105, Section 5.3.5 "b) The EAG asked for more details on technical verification in clarification question B24. The company provided internal validation and quality control checklists, but not the TECH-VER checklist despite a request by the EAG.⁴"	"b) The EAG asked for more details on technical verification in clarification question B24. The company provided internal validation and quality control checklists, ~~but not~~ which included a version of the TECH-VER checklist adapted to be more comprehensive. ~~despite a request by the EAG.~~⁴"	The internal validation checklist, used twice within the modelling process, was adapted from the TECH-VER checklist to be more comprehensive, and provided within the reference pack included with the submission of the CQ response. The provided files include both the initial internal validation checklist ('Clarification questions_internal_val_(Draft Global CEM) Iptacopan in C3G_21Aug24') and the final internal validation checklist ('Clarification questions_internal_val_(Submitted	Amended as follows: <i>"The EAG asked for more details on technical verification in clarification question B24. The company provided internal validation and quality control checklists, which included a comprised version of the TECH-VER checklist but not the full TECH-VER checklist despite a request by the EAG."</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		NICE CEM)_Iptacopan in C3G_10Mar25').	
Additional EAG analyses			
Page 107-108, Section 6.1.1.2 "2. Inclusion of wastage costs at iptacopan discontinuation (Section 4.2.9)"	"2. Inclusion of wastage costs at ~~iptacopan~~ SoC discontinuation (Section 4.2.9)"	Consideration of wastage costs for iptacopan was requested as part of the CQs and adopted by the company in the revised base case. The additional adjustment made by the EAG in their base case is to extend this approach to SoC, which should be reflected correctly.	Amended as follows: <i>"Inclusion of wastage costs at iptacopan and SoC discontinuation (Section 4.2.9)"</i> .
Page 18 and page 19, Section 1.6, Table 1.12 Page 111 and page 112, Section 6.2, Table 6.2 "Fixing violation (2 - per pack costing approach for iptacopan and SoC therapies)."	"Fixing violation (2 - per pack costing approach for ~~iptacopan~~ and extended to SoC therapies)."		Not a factual inaccuracy.
Page 108, Section 6.1.1.3 "5. Modelling of serious AEs (Section 4.2.7) Modelling all grade 3+ AEs ..."	"5. Modelling of ~~serious~~ severe AEs (Section 4.2.7) Modelling all grade 3+ AEs ..."	Serious AEs (SAEs) were included in the company base case. If the EAG prefers to include grade 3+ AEs instead, the terminology used to describe the EAG base case needs to be corrected to "severe" AEs.	Amended as proposed.

Section 3: Typographical and data errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21, Section 2, Table 2.1, Row 'Population', last column "There is some uncertainty as to the precise point in the care pathway and whether C3G recurrence post-transplant is included."	"There is some uncertainty as to the precise point in the care pathway when iptacopan would be used and whether C3G recurrence post-transplant is included."	Incomplete sentence.	Not a factual inaccuracy.
Page 31, Section 3.1.2, Table 3.1 "Table 3.1: Summary of key issues"	"Table 3.1: Eligibility criteria in the original SLR and SLR update "	Typographical error.	Corrected.
Page 31, Section 3.1.3 "The CS states that study Section occurred in two stages"	"The CS states that study ~~Section~~ selection occurred in two stages."	Typographical error.	Corrected.
Page 38, Section 3.2.21 "This submission only considers the adult cohort of the trial, in line with the patient population described in the decision."	"This submission only considers the adult cohort of the trial, in line with the patient population described in the decision problem. "	Typographical error.	Corrected.
Page 41, Section 3.2.2.2 "The phase 2 study is included to provide data on this clinical cohort"	"The phase 2 study is included to provide data on ~~this clinical cohort~~ patients with post-transplant recurrence of C3G... "	The rationale for including Phase 2 data in the submission is reported inaccurately (CS Section 2.5).	Amended.
Page 77, Section 3.2.7.4, Table 3.33, column 'Relationship to iptacopan'	Please merge the rows in the column 'Relationship to iptacopan column' to make clear that the text "Not suspected to be	Formatting error leads to ambiguity in not making clear that all SAEs and AEs were 'not suspected to be related to	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	related to iptacopan” applies to all rows of the table	iptacopan’ (see Table 11 of the CQ response).	
Page 100, Section 4.2.9.3.2, Table 4.7, Column ‘Weighted cost per annum’ £442.84 £442.84 £664.26 £885.68 £1,107.10 £1,107.10 £42,901.87 £8,119.33	£442.80 £442.80 £664.20 £885.60 £1,107.00 £1,107.00 £42,901.81 £8,119.25	The costs in Table 4.7 of the EAG report may have been calculated from the values reflected in the CS. Due to rounding of unit costs reported in the CS, the exact values used in the economic model differ slightly.	Not a factual inaccuracy. The EAG specifies that costs presented in Table 4.7 are comprised of costs taken from CS, Tables 47, 48, and 50.
Page 80, Section 3.3 “Comparative data versus eculizumab were not available from the iptacopan three clinical trial programme in C3G. Whilst eculizumab is considered of limited relevance as a comparator for this submission, the feasibility of an ITC was assessed for completeness. The clinical trials SLR (Appendix B) identified three trials which assessed eculizumab for C3G. However, none of the three studies reported eGFR results, the outcome of interest for the economic model. In addition, sample sizes were small, ranging	“Comparative data versus eculizumab were not available from the iptacopan ~~three~~ clinical trial programme in C3G. Whilst eculizumab is considered of limited relevance as a comparator for this submission, the feasibility of an ITC was assessed for completeness. The clinical trials SLR (Appendix B) identified three trials which assessed eculizumab for C3G. However, none of the three studies reported eGFR results, the outcome of interest for the economic model. In addition, sample sizes were small, ranging from 4–6 patients across each of the three trials. None of the studies were	Typographical errors – original text from the CS (page 79) reflected as a direct quote is not correctly reported.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
from 4–6 did not reflect the patient population who is eligible to receive eculizumab under the NHS England commissioning policy criteria. Overall, an ITC was not considered feasible.”	conducted in the UK, and thus did not reflect the patient population who is eligible to receive eculizumab under the NHS England commissioning policy criteria. Overall, an ITC was not considered feasible.”		

Section 4: Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 104, Section 5.2	“The probabilistic CS base-case analyses indicated cost effectiveness probabilities of ■% at WTP thresholds of £20,000 and £30,000 per QALY gained”	Please add confidentiality highlighting as indicated	Amended.

Section 5: Company modelling inaccuracies

Location in the model	Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Rows 21, 27:28 and 570:574 within the Control tab	Upon review of the EAG report and model, the company agrees that the economic model submitted with the CQ response contains errors related to the PSA. The company apologises for this oversight and thanks the EAG for highlighting it. When a model input is set to be ‘Not varied’ within the Control tab, the model assigns this input’s value to the hardcoded numeric base case	To ensure HSUVs are correctly varied during PSA in both the company and the EAG model, rows 22:26 and 566:568 within the Control tab should be deleted. This will prevent formulas from being replaced by static numeric values during the PSA, allowing the varied raw inputs to properly influence model outputs.	To ensure HSUVs are varied within the PSA.	Amended by company in addendum.

Location in the model	Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	value during the PSA simulations. As a result, if such an input is a formula dependent on other raw inputs (i.e., a live value) that are set to be varied, the raw input variations are overridden. Consequently, the varied raw inputs do not feed into the formula cell during the PSA, resulting in no impact on the model outputs. This issue affects the following parameters for health state utility values (HSUVs): <i>HSUVs for CKD stages 1–4</i> - Raw inputs (for linear regression coefficients): Rows 570:574 within the Control tab - Live/formula inputs: Rows 22:26 within the Control tab <i>Peritoneal dialysis</i> - Raw inputs: Row 566 within the Control tab - Live/formula inputs: Row 27 within the Control tab <i>Haemodialysis</i> - Raw inputs: Row 567 within the Control tab - Live/formula inputs: Row 28 within the Control tab	Please note that probabilistic results presented by the company are inaccurate due to this error. An amended model and corrected results can be provided to NICE and the EAG upon request.		

Location in the model	Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	<i>Post-transplant</i> - Raw inputs: Row 568 within the Control tab - Live/formula inputs: Row 21 within the Control tab			
Cell G2 within the Control tab	As part of the factual accuracy check of the EAG model, the company noticed an additional error in the PSA in the economic model submitted with the CQ response. The company apologises for this oversight. The formula in cell G2 currently uses 'COUNT' to determine the number of inputs to iterate over within the PSA. However, 'COUNT' only counts numerical entries and excludes non-numeric cells, causing the last row (row 574, containing the constant value used in the utility linear regression analysis) to be overlooked. As a result, this input is not included in the PSA iterations.	To correct this, please replace the 'COUNT' function with 'COUNTA' in cell G2. 'COUNTA' counts all non-empty cells, regardless of whether they contain numbers or text, ensuring that all PSA input rows are accurately counted, including the last row. Please note that probabilistic results presented by the company are inaccurate due to this error. An amended model and corrected results can be provided to NICE and the EAG upon request.	To ensure all parameters are varied correctly during the PSA process if they are set to be varied.	Amended by company in addendum.

Section 6: EAG modelling inaccuracies

Location in the model	Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Rows 22:26 within the Control tab	As part of the change in the EAG model relating to including the trial-derived health state utility values (HSUVs) within the PSA ("Fixing error (1 - [probabilistic analyses only] include CKD stage 1-4 utilities in PSA)"), the EAG set cells G22:G26 within the Control tab to a beta distribution and cells N22:N26 to 'Arbitrary'. These changes result in the inclusion of the trial-derived HSUVs for CKD stages 1-4 within the PSA (E15:E19, Utilities tab). However, the change made by the EAG means the variation from the mean of each trial-derived HSUV input for CKD stages 1-4 within the PSA is by the pre-defined arbitrary $\pm 20\%$. Given that the HSUV model inputs are based on linear regression coefficients, each with associated standard errors, the linear regression coefficients informing the trial-derived utilities should be varied in the PSA by their associated standard errors, instead of varying the trial derived utilities themselves by an arbitrary $\pm 20\%$.	The inputs within the Control tab for the trial-derived HSUVs for CKD stages 1-4 (rows 22:26) should be removed from the Control tab. Please also see Section 5: Company modelling inaccuracies. Probabilistic results presented by the EAG are considered inaccurate based on this modelling inaccuracy.	To correctly vary trial HSUVs for CKD stages 1-4 within the PSA	Amended by company in addendum.
Cell F18:F22 within the EAG tab	Within EAG adaptation "Fixing violation (2 - per pack costing approach for iptacopan and SoC therapies)", the EAG added calculations to capture treatment wastage of SoC therapies (F18:F22, EAG tab). In the company model, costs of SoC therapies are weighted by the proportion of patients receiving each therapy (F65:F69 of the Cost data tab). These weightings were not included by the	Calculations within cell F18:F22 of the EAG tab should include the proportion of patients on each SoC therapy. Results presented by the EAG including the adaptation "Fixing violation (2 - per pack costing	In order to correctly and consistently apply SoC treatment wastage costs within the economic model	Amended by EAG in addendum.

Location in the model	Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	EAG in their calculations of SoC wastage, resulting in 100% of patients incurring e.g. prednisolone wastage costs while only 32.4% of patients are modelled to receive prednisolone. As a result, costs of wastage of SoC therapies are overestimated by the EAG. Additionally, the EAG did not update cell C28 of the Base-case results tab (disaggregated costs) to capture the impact of the inclusion of SoC wastage on drug acquisition costs. This does not impact cost-effectiveness results but creates an inconsistency between disaggregated and total costs.	approach for iptacopan and SoC therapies)" are incorrect based on this modelling inaccuracy. In addition, the formula in cell C28 of the Base case results tab should be adjusted to be dependent on the selection in cell F5 of the EAG tab.		
Cell D9 within the EAG tab	The EAG report describes the exploratory scenario analysis 6 as: "6. Use of randomised comparison in APPEAR-C3G to inform eGFR slopes (Section 4.2.6). Estimating the eGFR slope for SoC and iptacopan using data from the randomised double-blind period of APPEAR-C3G." (page 108) However, the inputs selected in the EAG's model for this scenario differ from the description. Within cell D9 within the EAG tab, scenario 6 is described as '<i>Manual adjustment: Clinical data! C7 to "Analysis 1" from "Analysis 2"</i>' whereas the correct inputs for the scenario described above are	The description in D9 should be updated to '<i>Manual adjustment: Clinical data! C7 to "Analysis 3" from "Analysis 2"</i>'. Results currently presented in the EAG report for Scenario 6 are therefore incorrect based on selection of the wrong model inputs.	To ensure correct scenario results are generated and presented	Amended by EAG in addendum.

Location in the model	Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	included as “Analysis 3” in the economic model (Clinical data tab, row 12).			
Cell C10 within the EAG tab	Within cell C10 of the EAG tab, scenario 7 is described as ‘ <i>HD and PD KRT utilities based on Liem et al. (2008)</i> ’. The description is ambiguous as to whether the scenario also intends to use post-transplant utilities based on Liem et al. 2008, or only for HD and PD, with inconsistencies also present in the description of this scenario in the EAG report (see section on Key Issue 8: “(Face) validity of the chosen CKD stage 5+ utilities” and other utility inaccuracies).	The description in the model should be updated accordingly. In case post-transplant utilities from Liem et al. 2008 were not intended to be included in this scenario, changes in the model and correction of the scenario analysis results are required.	To clarify the inclusion of post-transplant utilities based on Liem et al. 2008	Description amended by EAG in addendum.
Multiple tabs	As part of changes made by the EAG, external workbook links have been introduced, attached to buttons controlling macros within the model	Remove all instances of external workbook links	To allow users to run macros without needing to open the VBA editor and will prevent error pop-ups related to external links	Not a factual inaccuracy.

References

1. Novartis. Data on File. Clinical expert input for Novartis’ response to iptacopan C3G EAG clarification questions, 2025.
2. Novartis. Data on File: Advisory Board Report - Clinical Interpretation of Data for Iptacopan in C3G. November 2024., 2024.
3. Novartis. Data on File: Clinical and Model Validation for Iptacopan in C3G, 2025.
4. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood, The Journal of the American Society of Hematology* 2013;121:4985-4996.
5. National Institute for Health and Care Excellence (NICE). Iptacopan for treating paroxysmal nocturnal haemoglobinuria (TA1000). Available at: <https://www.nice.org.uk/guidance/ta1000>. [Last accessed: October 2024], 2024.

6. Novartis. Data on File: A multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of iptacopan (LNP023) in complement 3 glomerulopathy (APPEAR-C3G). Clinical Study Report (Final CSR for adult data) v1.0, 2024.
7. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Available at: <https://www.nice.org.uk/process/pmg36>. [Last accessed: June 2025], 2025.