Iptacopan for treating complement 3 glomerulopathy

For screen – confidential information redacted

Technology appraisal committee D, 13 August 2025

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Iptacopan for treating complement 3 glomerulopathy

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

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Background on complement 3 glomerulopathy

C3G is a rare, chronic and progressive kidney condition leading to kidney failure

Causes

- Acquired or genetic autoimmune condition
- C3G is a rare kidney disease that is chronic (lifelong) and progresses (worsens) over time
- C3G is caused by part of the immune system, called the complement system, working incorrectly

Epidemiology

- 1-2 per million develop C3G annually in the UK, ~400 people with C3G in England, 179 eligible for iptacopan
- ~21 additional people diagnosed and eligible for iptacopan annually in England

Diagnosis and classification

- Median diagnosis age = 22 years, and 44% of diagnosed are under 18 years
- Kidney biopsy confirms C3G (and DDD or C3GN subtypes)

Symptoms and prognosis

- High protein in urine, blood in urine, reduced amount of urine, swelling of body
- Progressive, irreversible kidney damage and 50% chance kidney failure within 10 years

Abbreviations: C3G, complement 3 glomerulopathy; DDD, dense deposit disease; C3GN, complement 3 glomerulonephritis.

Patient perspectives

First treatment to combat lifelong C3G and delay dialysis is welcomed

Submissions from KRUK, MPGN/DDD Support Group, and patient expert

- C3G is difficult to diagnose, has no cure and current treatments are inadequate
- Deterioration from C3G (and dialysis) is physically and mentally taxing
- Iptacopan offers effective first treatment which delays burdensome, costly dialysis and kidney transplants – new kidneys also susceptible to C3G damage
- Iptacopan can mitigate disruption of C3G (and dialysis) to HRQoL and employment prospects of people with C3G and families
- Ease of administration and minimal side effects of iptacopan is welcome
- People with C3G feel let down by lack of treatment options, after-care (e.g. mental health resources) and clinicians' understanding of C3G
- C3G is so rare that there is no one else to talk to about it

> 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 schooling, career choice and where you live.

> [iptacopan] gives patients hope… being told there was no cure or treatment was devastating

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Abbreviations: C3G, complement 3 glomerulopathy; KRUK, Kidney Research UK; MPGN, membranoproliferative glomerulonephritis; DDD, dense deposit disease; HRQoL, health-related quality of life.

Equality considerations

Understanding of C3G varies regionally, C3G impact and kidney transplant access varies by ethnic and socio-economic background

- C3G is usually diagnosed in earlier adulthood but it impacts people of all ages – current marketing authorisation limits iptacopan use to adults only
- C3G is uncommon and the familiarity/understanding of the condition varies across renal centre specialists
- Burden of C3G may disproportionately impact black and minority groups, and those from lower socio-economic backgrounds
- Black people and people from Asian family backgrounds may have longer waiting times for kidney transplants compared to white people

Abbreviations: C3G, complement 3 glomerulopathy.

Clinical perspectives

Iptacopan targets underlying condition and demonstrates benefit over current care

Submissions from NHSE, UKKA, UKRPG and clinical experts

- Very limited treatment options for this population – significant unmet need
- C3G diagnosed young, has poor prognosis and kidney failure within 5-10 years
- Care of people with C3G managed in local renal centres but some managed by NHSE highly specialised service pathway
- No defined clinical pathway, care informed by KDIGO guideline & NRCTC guidance
- Iptacopan could be a step-change as trials show reduction in proteinuria
- Trial safety data is good – data from PNH and compassionate use in C3G confirms
- Limited trial evidence that iptacopan may work post-transplant
- Acute eGFR <30, excluded by trials, may have worse prognosis but could benefit
- Iptacopan increases risk of bacterial infection, so additional vaccinations needed
- Toxicity of corticosteroids and toxicity monitoring of MMF not applicable to iptacopan

Hugely needed targeted treatment for shutting off C3 glomerulopathy disease

Formalising of pathway needed if iptacopan is recommended

Would additional resource be required to implement iptacopan in the NHS?

Abbreviations: NHSE, NHS England; UKKA, UK Kidney Association; UKRPG, UK Renal Pharmacy Group (part of the UKKA); C3G, complement 3 glomerulopathy; KDIGO, Kidney Disease Improving Global Outcomes; NRCTC, National Renal Complement Therapeutics Centre; PNH, paroxysmal nocturnal haemoglobinuria; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil.

Iptacopan (Fabhalta®, Novartis)

Marketing authorisation	• Marketing authorisation is 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. • MHRA MA for this indication was sought in March 2025 via the International Recognition Procedure with the EMA as reference regulator and approved in May 2025
Mechanism of action	• In C3G, overactivation of the complement alternative pathway leads to deposition of C3 within the glomeruli, triggering inflammation and glomerular injury. • 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.
Administration	Iptacopan 200 mg capsules are taken orally twice daily
Price	• List price of iptacopan is £26,500.00 per 56-capsule pack • A patient access scheme is applicable

Abbreviations: C3G, complement 3 glomerulopathy; RAS, renin-angiotensin inhibitor; MHRA, Medicines and Healthcare products Regulatory Agency; MA, marketing authorisation.

Key issues

Issue	Resolved?	ICER impact
Inclusion of post-transplant C3G recurrence subgroup in the decision problem	No	Unknown
Relevance of eculizumab as a comparator for highly aggressive post-transplant C3G recurrence subgroup	No	Unknown
Data used for eGFR slopes to model transitions	No	Large
Constant eGFR progression independent of CKD stage	No	Large
Modelling of treatment discontinuation	No	Unknown
Constant treatment effect for iptacopan	No	Unknown
Validity of chosen CKD stage 5+ utilities	No	Large

Other issues to be discussed which may not be resolvable (see model structure slides)

- Most QALYs & costs accrue beyond trial length
- Details of expert input unclear

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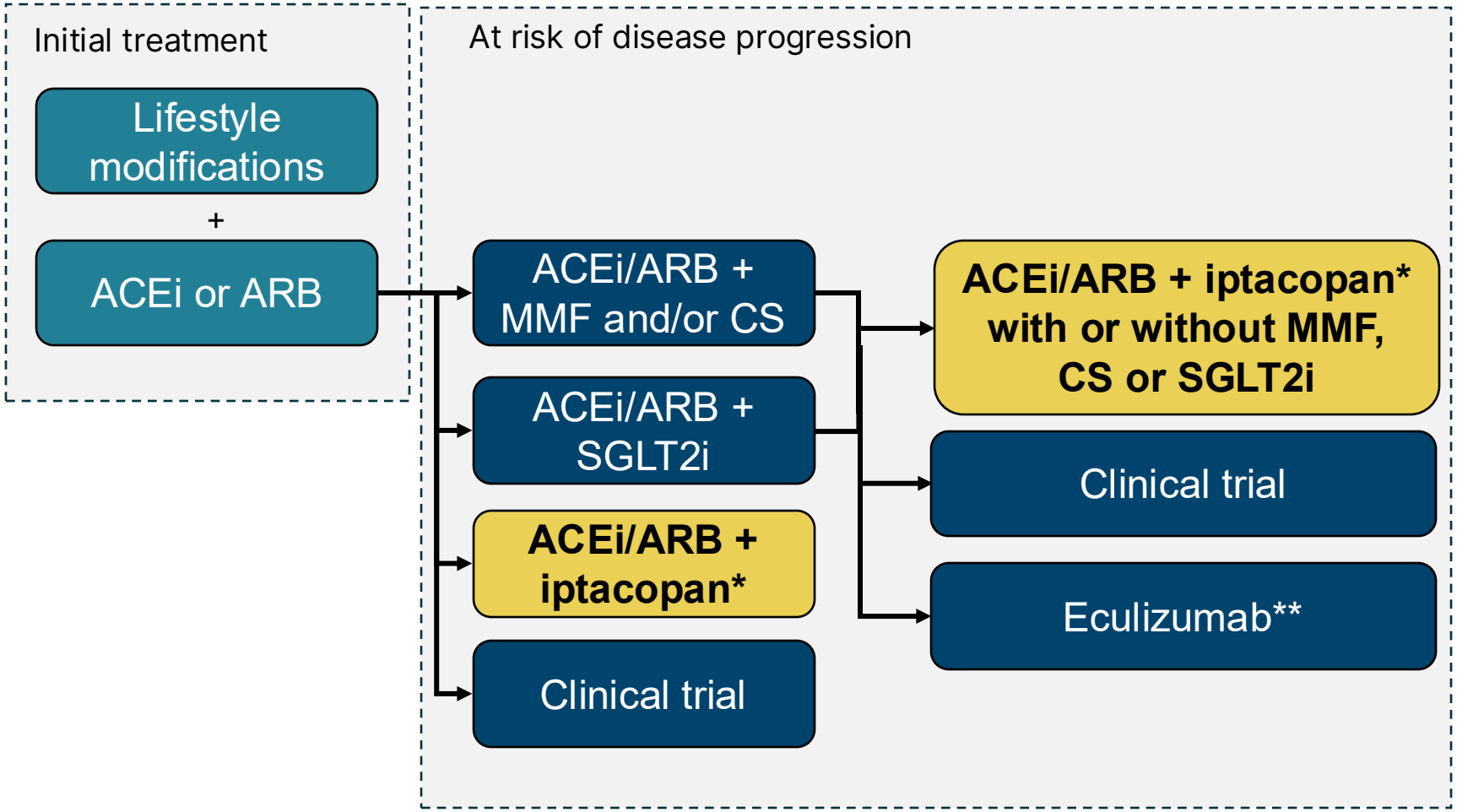
Abbreviations: ICER, incremental cost effectiveness ratio; C3G, complement 3 glomerulopathy; eGFR, estimate glomerular filtration rate; CKD, chronic kidney disease; QALY, quality-adjusted life year.

Treatment pathway



- Iptacopan would be offered alongside a maximally tolerated dose of an ACEi or ARB
- Clinician statements indicate that iptacopan may displace MMF and CS

** NHSE commissioning permits certain off-label use of eculizumab for post-transplant recurrence

* ACEi/ARBs used in combination unless otherwise contraindicated or not tolerated

Does the pathway reflect current UK clinical practice?

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Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MMF, mycophenolate mofetil; CS, corticosteroids; SGLT2i, sodium-glucose cotransporter-2 inhibitors; NHSE, NHS England.

Key issues: Inclusion of post-transplant C3G recurrence subgroup in the decision problem

Background

- NICE scope included subgroup analysis of native and transplant C3G where evidence allows
- EAG is unclear if the post-transplant population who experience C3G recurrence should be included in the eligible population because no comparative data has been provided for this subgroup

Company

- Evidence from phase III APPEAR-C3G was presented for native C3G and this was used to inform CEA
- Although the phase II trial included post-transplant C3G recurrence, the small sample size (N=11) was insufficient to robustly inform post-transplant subgroup CEA
- UK clinicians advised company that native data would be transferable to post-transplant group due to the same C3G MOA before and after kidney transplant
- Post-transplant subgroups have not been excluded from prior CKD appraisals' recommendations (TA942, TA937, TA890 and more) when only native kidney data was presented

EAG comments

- No comparison of post-transplant subgroup has been performed, and appropriate comparator is unclear
- Despite data limitations, ITC and CEA of post-transplant C3G recurrence subgroup is useful

Is the evidence presented generalisable to the post-transplant C3G recurrence group?

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Abbreviations: C3G, complement 3 glomerulopathy; EAG, external assessment group; CEA, cost-effectiveness analysis; MOA, mechanism of action; CKD, chronic kidney disease; TA, technology appraisal; ITC, indirect treatment comparison.

Iptacopan for treating complement 3 glomerulopathy

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Key issues: Relevance of eculizumab as a comparator for HA post-transplant C3G recurrence subgroup

Background

- Eculizumab routinely commissioned off-label by NHSE for treating C3G recurrence post-transplant
- Although eculizumab may be a relevant comparator, there has been no (direct or indirect) comparison of clinical effectiveness in the post-transplant group who experience highly aggressive C3G recurrence
- EAG wants comparison if common outcomes allow, company says ITC unfeasible due to trial differences

Company

- UK clinicians advised iptacopan would be started before eculizumab – eculizumab requires highly aggressive (>20% eGFR drop in 3 months) recurrent disease in a person with a kidney transplant, but iptacopan would be started on diagnosis of recurrence
- SLR identified 3 eculizumab trials but eGFR not reported and inclusion criteria differed from NHSE CCP
- ITC deemed unfeasible, eculizumab trials not in UK, max. 6 participants, lacked eGFR, and proteinuria criteria required elevated proteinuria (while phase II iptacopan enrolled low/normal proteinuria at baseline)
- Considers lack of ITC minor limitation as limited use of eculizumab in UK practice (1 per year since 2017)

EAG comments

- Asked for ITC of common outcomes (e.g. proteinuria) of eculizumab trials and phase II trial of iptacopan
- Acknowledged differences in trial populations and agreed with company that ITC would not be meaningful
- Eculizumab comparative evidence needed, unless iptacopan offered earlier than eculizumab eligibility

Is further data and analysis required to evaluate iptacopan's clinical effectiveness relative to eculizumab?

Abbreviations: HA, highly aggressive; C3G, complement 3 glomerulopathy; NHSE, NHS England; EAG, external assessment group; ITC, indirect treatment comparison; eGFR, estimated glomerular filtration rate; SLR, systematic literature review; CCP, clinical commissioning policy.

APPEAR-C3G trial results

Iptacopan reduces proteinuria and improves eGFR compared to placebo

Primary Outcome

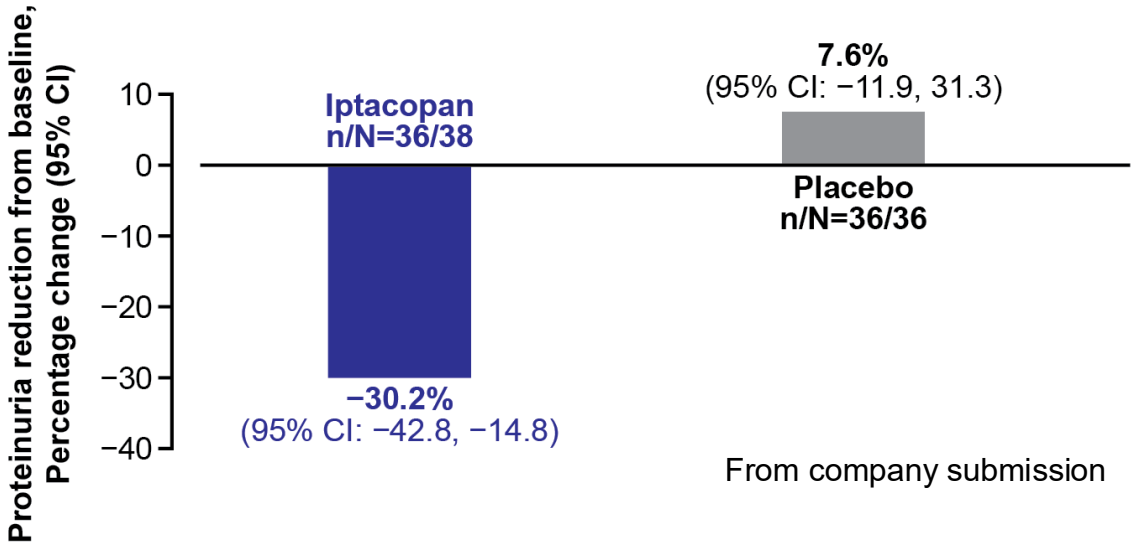
- Iptacopan showed a 35.1% (95% CI: 13.8% to 51.1%, p<0.01) reduction in proteinuria at 6 months compared with placebo.
- During open-label period (months 6-12):
  - iptacopan-iptacopan group sustained 6-month drop in proteinuria out to 12 months
  - placebo-iptacopan group experienced similar reduction in months 6-12 as iptacopan double-blind group in months 0-6.

Secondary Outcome

At 6 months, average eGFR change from baseline in iptacopan group was numerically 2.16 (95% CI: -2.75 to 7.06; p=0.19) higher than placebo group

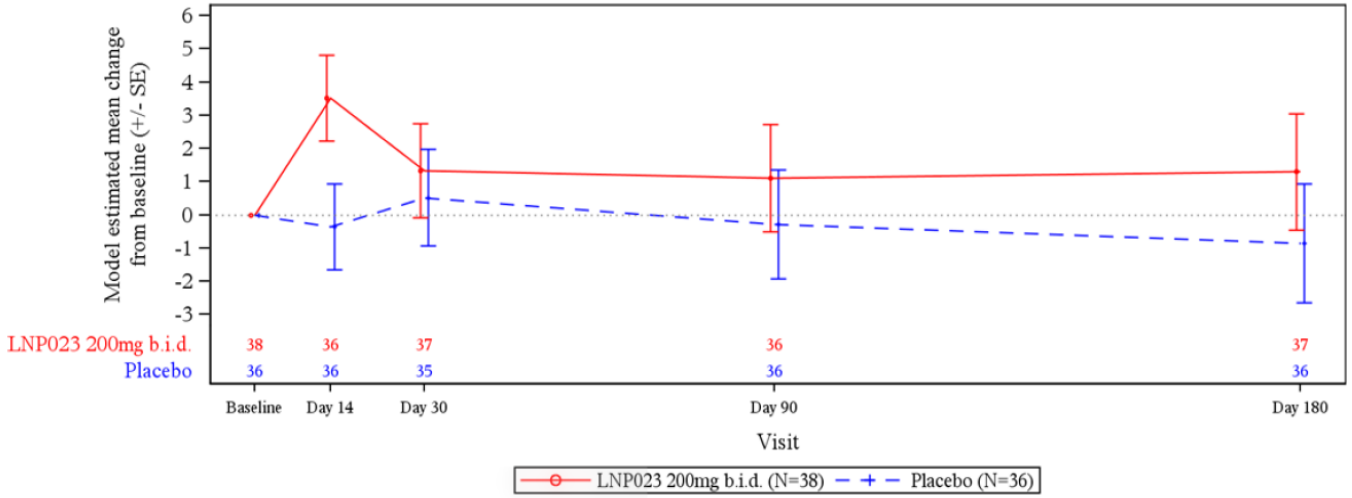
See appendix for further study details

Proteinuria reduction at 6M from baseline (FAS)



From company submission

Mean eGFR change at 6M from baseline up to 6M (FAS)



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Abbreviations: C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; CI, confidence interval; 6M, 6 month; FAS, full analysis set.

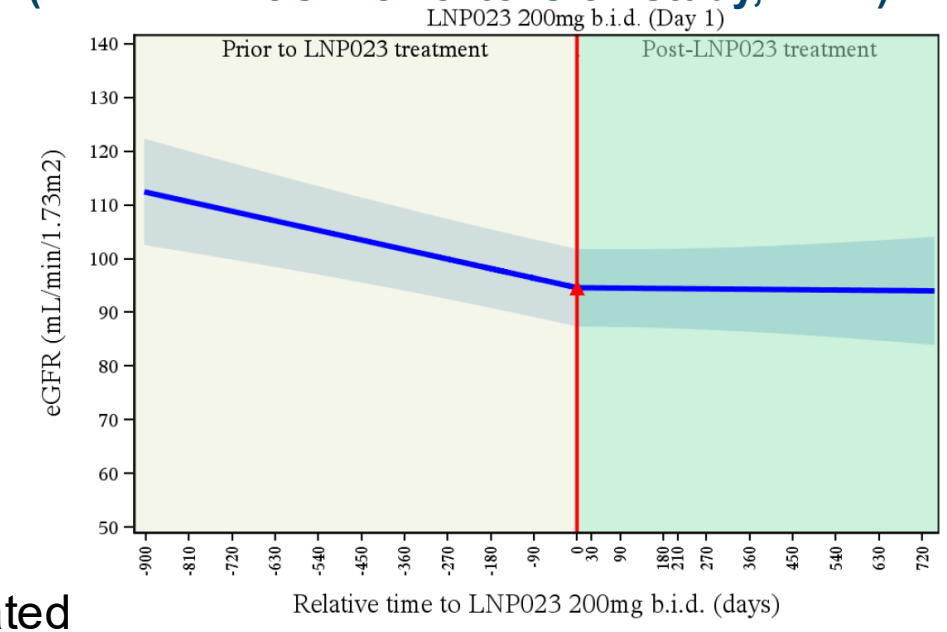
APPEAR-C3G trial results

eGFR slope change indicates eGFR decline stabilisation on iptacopan

Exploratory endpoint analysed the rate of eGFR decline (mean annual eGFR slope change) before iptacopan and on-iptacopan

- Mean annual **pre-iptacopan** slope of **-7.22 mL/min/1.73m²** (95% CI: -10.10 to -4.35)
- Mean annual **on-iptacopan** slope of **-0.29 mL/min/1.73m²** (95% CI: -3.88 to 3.31)
- So, taking iptacopan resulted in a mean reduction in annual eGFR slope decline of **6.94 mL/min/1.73m²** (95% CI: 3.48 to 10.39; p=0.0001) compared to pre-iptacopan treatment

Mean annual eGFR slope change with iptacopan (APPEAR-C3G incl. extension study, n=74)



From company submission

Adverse events

Approximately half of SAEs in broad safety set were infection related

	Controlled safety set (6-month double-blind placebo-controlled period of APPEAR-C3G)		Broad safety set (all iptacopan C3G studies)
	Iptacopan (N=38)	Placebo (N=36)	Iptacopan (N=101)
Number of patients with at least one SAE, n (%)	3 (7.9)	1 (2.8)	20 (19.8)

Abbreviations: C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; CI, confidence interval; SAE, serious adverse event.

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Model structure

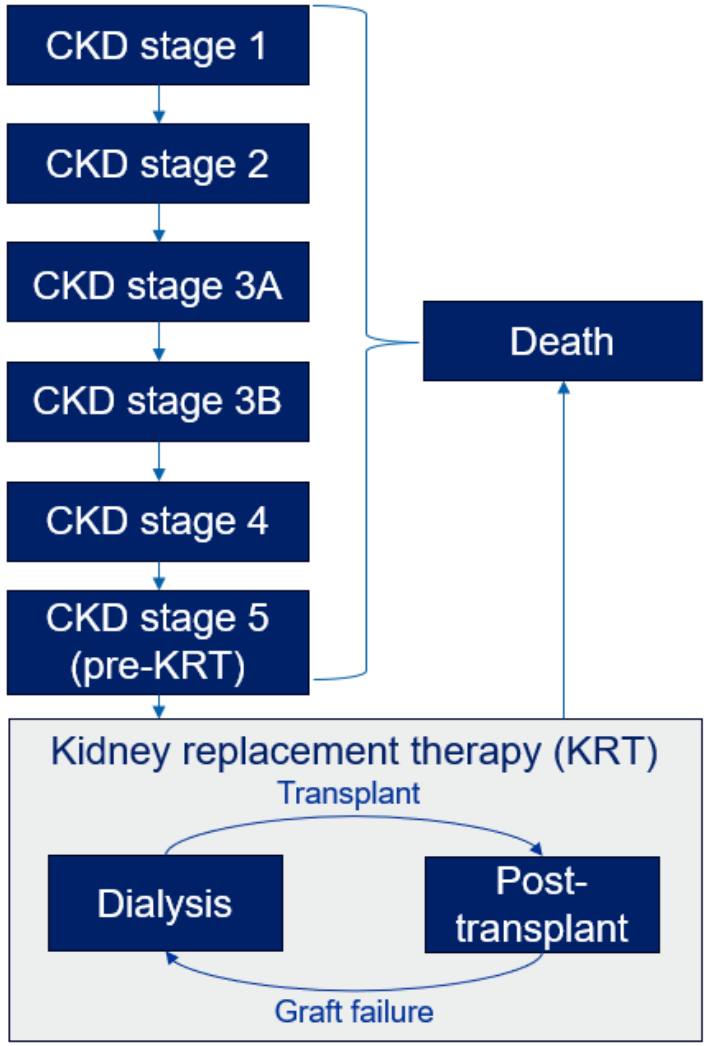
Costs and QALYs strongly driven by dialysis

Markov model where cohort progresses through CKD stages to kidney replacement therapy (KRT) and death

- Due to trial data limitations (small sample, no progression to later CKD stages), eGFR slope has been used to estimate CKD stage transitions
- 3-month cycles with a lifetime horizon = 72.1 years
- 'No improvement' assumption, can't move back, e.g. CKD 3A → CKD 2
- Receives KRT upon eGFR threshold = ≤7.6 mL/min/1.73 m^2 (base case)
- Model does not allow iptacopan use post-transplant

Clinical experts, are the following transplant assumptions reasonable?

- Model allows for multiple transplants and graft failures over lifetime
- Average lifetime transplants is 1.9 for SoC versus 1.5 for iptacopan



From company submission

Abbreviation: QALY, quality-adjusted life year; CKD, chronic kidney disease; KRT, kidney replacement therapy (dialysis or kidney replacement); eGFR, estimated glomerular filtration rate; SoC, standard of care.

Model structure

Costs and QALYs strongly driven by dialysis

QALY key drivers

- Transitions between CKD-stage health states are driven by eGFR slope in each arm and QALYs accrue in the different CKD stages
- Iptacopan's benefit comes from delaying progression to later CKD stages or KRT, and avoiding the consequent drops in HRQoL

Costs key drivers

- Costs are captured through treatment (acquisition) costs and health state costs
- Iptacopan costs strongly driven by treatment costs
- SoC costs strongly driven by dialysis costs

Summarised EAG modelling issues

- Model relies on extrapolating data beyond trials' length (SoC = 2.5 years, iptacopan = 2 years), costs and QALYs disproportionately accrue across arms for observed period versus longer extrapolated period (see appendix)
- EAG concerned by iptacopan extrapolation benefit = higher % of total QALYs and lower % of total costs accrued in the extrapolated period for iptacopan compared with SoC, model mechanism causing this unclear

- Company sought clinical advice (e.g. on clinical interpretation of data for iptacopan in C3G) and shared a report from their ad board and summaries of discussions which have informed model assumptions
- EAG concerned by lack of full details limiting full scrutiny of advice and consequent modelling assumptions

Is the model structure appropriate?

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Abbreviation: QALY, quality-adjusted life year; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy (dialysis or kidney replacement); HRQoL, health-related quality of life; SoC, standard of care; EAG, external assessment group; C3G, complement 3 glomerulopathy.

Key Issue: Data used for eGFR slopes to model transitions (1/2)

Background

- Company used eGFR slope, not observed CKD stage changes, to model transitions between CKD stages
- eGFR slope based on before-after comparison from APPEAR-C3G including open-label extension study
- EAG believes company's data for generating eGFR slopes lacks randomisation and may introduce bias

Company

- Small sample size prohibits modelling of CKD stage transitions from observed transitions in APPEAR-C3G
- Ad board said placebo eGFR slope generated from 6M APPEAR-C3G inconsistent with C3G SoC literature and clinical practice – extrapolation predicts 25.7 years time to kidney failure. National Registry of Rare Kidney Diseases (RaDaR) UK registry data show median is ~10 years
- More credible is pre-iptacopan (across trial arms) eGFR data which predicts SoC kidney failure 10-11 years

EAG comments

- For SoC eGFR slope, prefer to use:
  - 1) **RaDaR data – EAG base case**, or 2) placebo arm data from 6M APPEAR-C3G – EAG scenario
- For iptacopan, apply treatment effect observed in randomised double-blind period of APPEAR-C3G to RaDaR-based SoC slope to inform the iptacopan eGFR slope
- Preserves the treatment effect from only the randomised double-blind part of APPEAR-C3G
- Both EAG approaches lead to substantial increases in ICER

Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; C3G, complement 3 glomerulopathy; EAG, external assessment group; 6M, 6 month; SoC, standard of care; RaDaR, National Registry of Rare Kidney Disease; ICER, incremental cost effectiveness ratio.

See appendix for approaches to baseline data

Key Issue: Data used for eGFR slopes to model transitions (2/2)

Approach	SoC arm details	Iptacopan arm details	SoC	Iptacopan	Iptacopan treatment effect
Company base case	APPEAR-C3G, up to 2.5 years, pre-iptacopan (N=74)	APPEAR-C3G, up to 2 years, on-iptacopan (N=74)	-7.22 (-10.10 to -4.35)	-0.29 (-3.88 to 3.31)	6.94 (3.48 to 10.39)
Company scenario	APPEAR-C3G, 6M double-blind period only, placebo arm (N=36)	APPEAR-C3G, 6M double-blind period only, iptacopan arm (N=38)	-3.08 (-10.13 to 3.97)	-0.03 (-6.93 to 6.88)	3.05 (-6.82 to 12.92)
Company scenario	APPEAR-C3G + Phase II native kidney cohort pooled, up to 2.5 years, pre-iptacopan (N=90)	APPEAR-C3G + Phase II native kidney cohort pooled, up to 4.7 years, on-iptacopan (N=90)	-8.32 (-10.89 to -5.74)	-0.70 (-3.77 to 2.36)	7.62 (4.62 to 10.62)
EAG base case	RaDaR C3G population (N=139)	APPEAR-C3G, 6M, iptacopan treatment effect applied to RaDaR (N=38)	-4.00 (-5.4, -2.6)	-0.95 (NR)	3.05 (-6.82 to 12.92)

eGFR slope units = mL/min/1.73m^2/year

What is committee's preferred approach for generating eGFR slopes for model transitions?

Abbreviations: eGFR, estimated glomerular filtration rate; SoC, standard of care; C3G, complement 3 glomerulopathy; RaDaR, National Registry of Rare Kidney Diseases; NR, not reported.

Key Issue: Constant eGFR progression independent of CKD stage

Background

- Company's model assumes that eGFR declines at a constant rate regardless of current CKD stage
- EAG doubts speed of eGFR progression is independent of CKD stage and constant over modelled horizon

Company

- Sample size of iptacopan trials prohibits estimation of CKD-stage dependent eGFR decline rates
- Clinical ad board advised that eGFR slope would fluctuate, but the overall trajectory is progressive decline, and a linear slope was a reasonable simplification
- At CQ, clinicians confirmed linear slope appropriate and eGFR decline does not steepen closer to KRT

EAG comments

- Unrealistic assumption used which likely under/overestimates people's modelled eGFR declines
- Recommended approaches were not adopted
  1. CKD-stage dependent eGFR decline rates from iptacopan C3G trials
  2. Time-dependent eGFR decline rates from iptacopan C3G trials
- Company assumption may inaccurately model long-term cost effectiveness – especially for KRT

Does a linear (constant) slope model eGFR progression appropriately across CKD-stages? What is committees preferred approach and is further analysis required?

Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; EAG, external assessment group; CQ, clarification questions; KRT, kidney replacement therapy (dialysis or transplant); C3G, complement 3 glomerulopathy.

Key issue: Modelling of treatment discontinuation

Background

- Annual treatment discontinuation rate for iptacopan for those who have not reached kidney failure of 0.063 (from broad safety set, n=101; 1.57% per 3-month cycle) is applied constantly over time
- EAG questions constant treatment discontinuation rate while on iptacopan prior to kidney failure, so requested time-varying discontinuation rates analyses

Company

- Constant treatment discontinuation derived from all-cause discontinuation in pooled iptacopan trials set
- At CQ, company provided TTD analyses for APPEAR-C3G only and pooled iptacopan trials
- Best-fit exponential and log-normal curves used in scenarios and impacted ICERs modestly

EAG comments

- Constant rate over time seems implausible
- Concerned that presented TTD scenarios impact ICER more if iptacopan waning assumption applied
- Clinician input and curve selection details lacking, company must detail per NICE DSU TSD 14 for EAG to scrutinise

Which modelling approach is appropriate for treatment discontinuation of iptacopan?

See appendix for details

Abbreviations: EAG, external assessment group; CQ, clarification questions; TTD, time to treatment discontinuation; ICER, incremental cost effectiveness ratio; DSU, decision support unit; TSD, technical support document.

Key issue: Constant treatment effect for iptacopan

Background

- While people remain on iptacopan treatment, they benefit from a constant treatment effect (no waning)
- EAG says constant iptacopan treatment effect over the model horizon has been inadequately justified

Company

- Iptacopan disease-modifying treatment effect was sustained throughout APPEAR-C3G and extension study
- Clinical experts say that treatment effect is not expected to wane
- Not feasible to determine potential treatment waning from APPEAR-C3G due to few CKD-stage changes

EAG comments

- Iptacopan treatment effect not waning over 71.1-year time horizon lacks sufficient justification
- EAG's clinical expert agreed that on-target effect on complement inhibition remains similar over time
- Treatment effect waning scenario (beyond observed trial length) was requested and should be explored
  - Formal comparison needed incl. tabulated TTE data, KM plots, cumulative hazard plots
- Expects that waning of treatment effect would somewhat increase the ICER

Does committee prefer a constant treatment effect or waning treatment effect approach?

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Abbreviations: EAG, external assessment group; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; TTE, time to event; KM, Kaplan-Meier; ICER, incremental cost effectiveness ratio.

Key issue: Validity of chosen CKD stage 5+ utilities (1/2)

Background

- Company used EQ-5D-5L mapped to EQ-5D-3L from APPEAR-C3G for CKD 1-4, Jesky 2016 for CKD 5 (pre-KRT) & Lee 2005 for KRT – studies have been used in prior CKD appraisals
- Jesky 2016 and Lee 2005 used broadly across historic CKD appraisals and are not specific to C3G
- EAG considers company's literature-based CKD stage 5+ utilities low and suggests alternatives

Company

- APPEAR-C3G used for CKD 1-4, as 5+ not available from trial, supplemented with Jesky 2016 & Lee 2005
- Age adjustments applied to literature-based utilities to account for C3G/general CKD population differences
- Liem 2008 meta-analysis biased by trial differences & marginal HD/PD (0.56/0.58) difference is a concern

EAG comments

- Concerned by steep decline in modelled utilities from CKD 4 (0.85) to 5+ (0.49 to 0.81)
- Despite company's age- and sex-adjustment, Lee 2005 (older, wider CKD population) modelled values inadequately represent younger C3G population, EAG prefers Liem 2008 adjusted (0.86) post-transplant
- Suggests validating utilities using detail from prior TAs and values from Liem 2008 or recent Sinha 2025
- Scenario using 0.86 from Liem 2008 adjusted shows higher CKD stage 5+ utilities will increase the ICER

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Abbreviations: CKD, chronic kidney disease; SLR, systematic literature review; EQ-5D-5L(-3L), EuroQol 5-dimension 5-level (3-level) questionnaire; C3G, complement 3 glomerulopathy; KRT, kidney replacement therapy (dialysis or transplant); EAG, external assessment group; HD, haemodialysis; PD, peritoneal dialysis; RCT, randomised controlled trial; TA, technology appraisal; ICER, incremental cost effectiveness ratio.

Key issue: Validity of chosen CKD stage 5+ utilities (2/2)

Economic model inputs for the company base case

Health state	Reported utility value for study population (95% CI)	Source	Modelled utility at baseline
CKD stage 1	0.91	APPEAR-C3G	0.91
CKD stage 2	0.91		0.91
CKD stage 3a	0.86		0.86
CKD stage 3b	0.86		0.86
CKD stage 4	0.85		0.85
CKD stage 5 (pre-KRT)	0.73 (0.62 to 1.00)	Jesky et al. 2016	0.81**
Haemodialysis	0.44 (SD: 0.32)*	Lee et al. 2005	0.49**
Peritoneal dialysis	0.53 (SD: 0.34)*		0.58**
Post-transplant	0.71 (SD: 0.27)*		0.76**

* EAG scenario used Liem 2008 values for haemodialysis (0.56), peritoneal dialysis (0.58) and transplant (0.81)

** Modelled values for CKD stage 5 onwards vary from reported values due to age- and sex-adjustment for C3G

On SoC, people are modelled to spend more time in higher CKD stages, so CKD 5+ utilities disproportionately impact SoC benefits

- Company's CE advised that 0.76 post-transplant is "relatively low" and supported 0.86 (Liem 2008 adjusted)
- EAG used 0.76 in base case

What source of utilities does committee prefer to represent CKD stage 5+ utilities?

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; KRT, kidney replacement therapy (dialysis or transplant); SoC, standard of care; CE, clinical expert; EAG, external assessment group; C3G, complement 3 glomerulopathy.

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Source of baseline patient characteristics	APPEAR-C3G	RaDaR
Sources for eGFR slopes	• **SoC** used APPEAR-C3G trial pre-iptacopan data, up to 2.5 years (N=74) • **Iptacopan + SoC** used APPEAR-C3G trial on-iptacopan data, up to 2 years (N=74)	• **SoC** used RaDaR C3G population data (N=139) • **Iptacopan + SoC** applied the treatment effect from 6-month randomised double-blind period of APPEAR-C3G trial to the SoC RaDaR slope
Modelling of AEs	Serious AEs suspected to be related to iptacopan use from the broad safety set (N=101)	All grade 3+ AEs regardless of relationship to iptacopan use from the controlled safety set (N=74)

Abbreviations: EAG, external assessment group; C3G, complement 3 glomerulopathy; RaDaR, National Registry of Rare Kidney Disease; eGFR, estimated glomerular filtration rate; SoC, standard of care; AE, adverse event.

Cost-effectiveness results summary

- Cost effectiveness results cannot be reported here because of confidential discounts for included technologies
- Company base case ICER and EAG base case ICER are substantially above NICE's usual cost-effectiveness threshold

- All results are presented in Part 2 slides for committee

Abbreviations: ICER, incremental cost effectiveness ratio; EAG, external assessment group.

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- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Uncaptured benefits

- Iptacopan may have uncaptured benefits including:
    - Delayed progression to higher CKD stages, especially delaying the need for dialysis or kidney replacement
        - Benefit to both C3G population and broader CKD population needing KRT
    - If iptacopan could be used post-transplant, this is presently not captured by the modelling

Remaining uncertainty

- Due to some assumptions which underpin the model relying on company clinicians' advice which has not been presented to the EAG in all cases for complete scrutiny

Managed access

- No managed access proposal has been submitted by the company and there are no plausibly cost-effective ICERs

Abbreviations: CKD, chronic kidney disease; C3G, complement 3 glomerulopathy; KRT, kidney replacement therapy (dialysis or kidney transplant); EAG, external assessment group; ICER, incremental cost effectiveness ratio.

Iptacopan for treating complement 3 glomerulopathy

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

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Key issues

Key issue	ICER impact	Slide
Inclusion of post-transplant C3G recurrence subgroup in the decision problem	Unknown	10
Relevance of eculizumab as a comparator for HA post-transplant C3G recurrence subgroup	Unknown	12
Data used for eGFR slopes to model transitions	Large	18
Constant eGFR progression independent of CKD stage	Large	20
Modelling of treatment discontinuation	Unknown	21
Constant treatment effect for iptacopan	Unknown	22
Validity of chosen CKD stage 5+ utilities	Large	23

Abbreviations: ICER, incremental cost effectiveness ratio; C3G, complement 3 glomerulopathy; HA, highly aggressive; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Iptacopan for treating complement 3 glomerulopathy

Supplementary appendix

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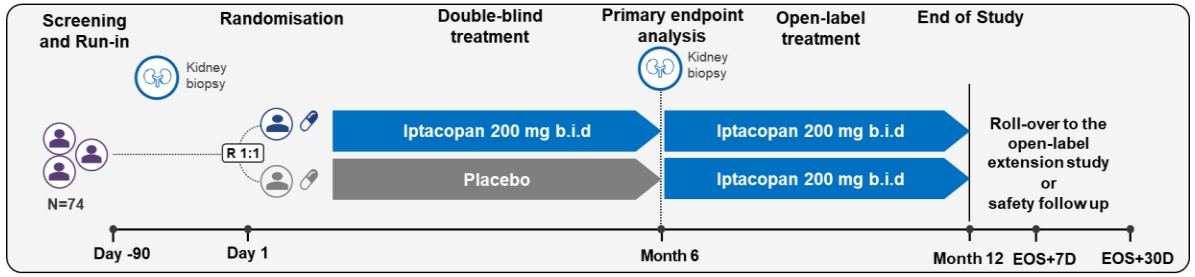
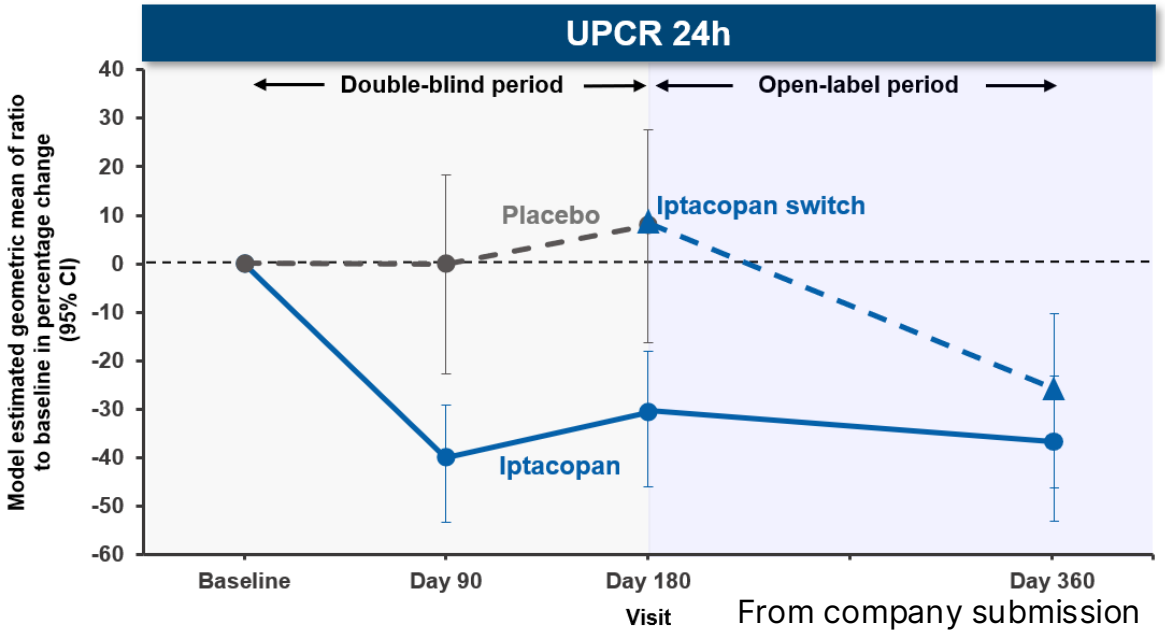
APPEAR-C3G study

APPEAR-C3G study design



Primary outcome: 24h UPCR change from baseline up to 12 months



From company submission

Geometric mean ratio of change from baseline in 24h UPCR up to month 12 by treatment group (FAS)

Visits	Iptacopan (95% CI)	Placebo-iptacopan switch (95% CI)
Day 180	0.66 (0.51 to 0.85)	1.09 (0.92 to 1.28)
Day 360	0.60 (0.45 to 0.80)	0.73 (0.58 to 0.92)

Abbreviations: C3G, complement 3 glomerulopathy; EOS, end of study; UPCR, urine protein-to-creatinine ratio; FAS, full analysis set.

Baseline patient characteristics in the model

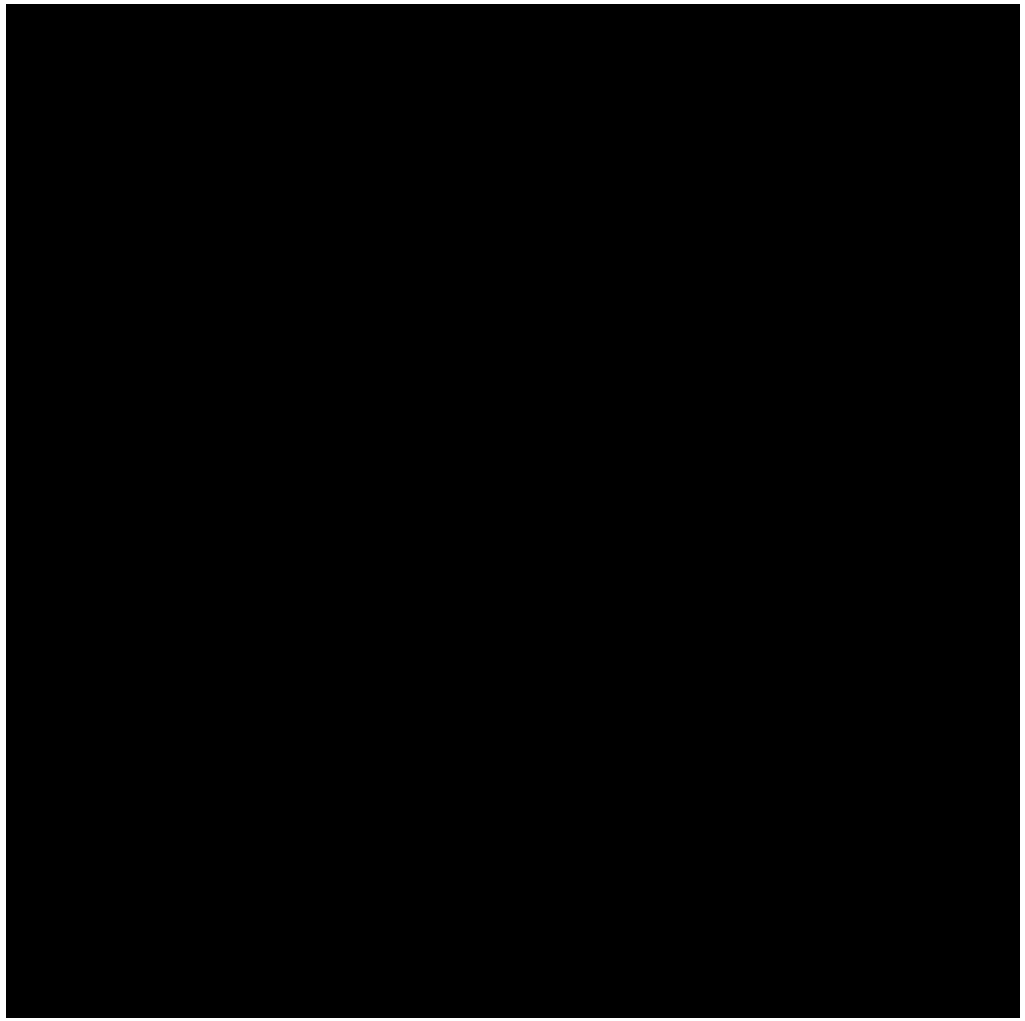
Company base case uses APPEAR-C3G data, EAG uses RaDaR data

Parameter	APPEAR-C3G (company base case)	RaDaR (EAG base case)
Baseline age, years	27.9	28.9
Proportion female	36.5%	46.1%
Mean eGFR mL/min/1.73m^2	92.8	78.2
CKD stage 1	58.1%	38.4%
CKD stage 2	23.0%	27.3%
CKD stage 3a	6.8%	10.1%
CKD stage 3b	9.5%	14.1%
CKD stage 4	2.7%	10.1%

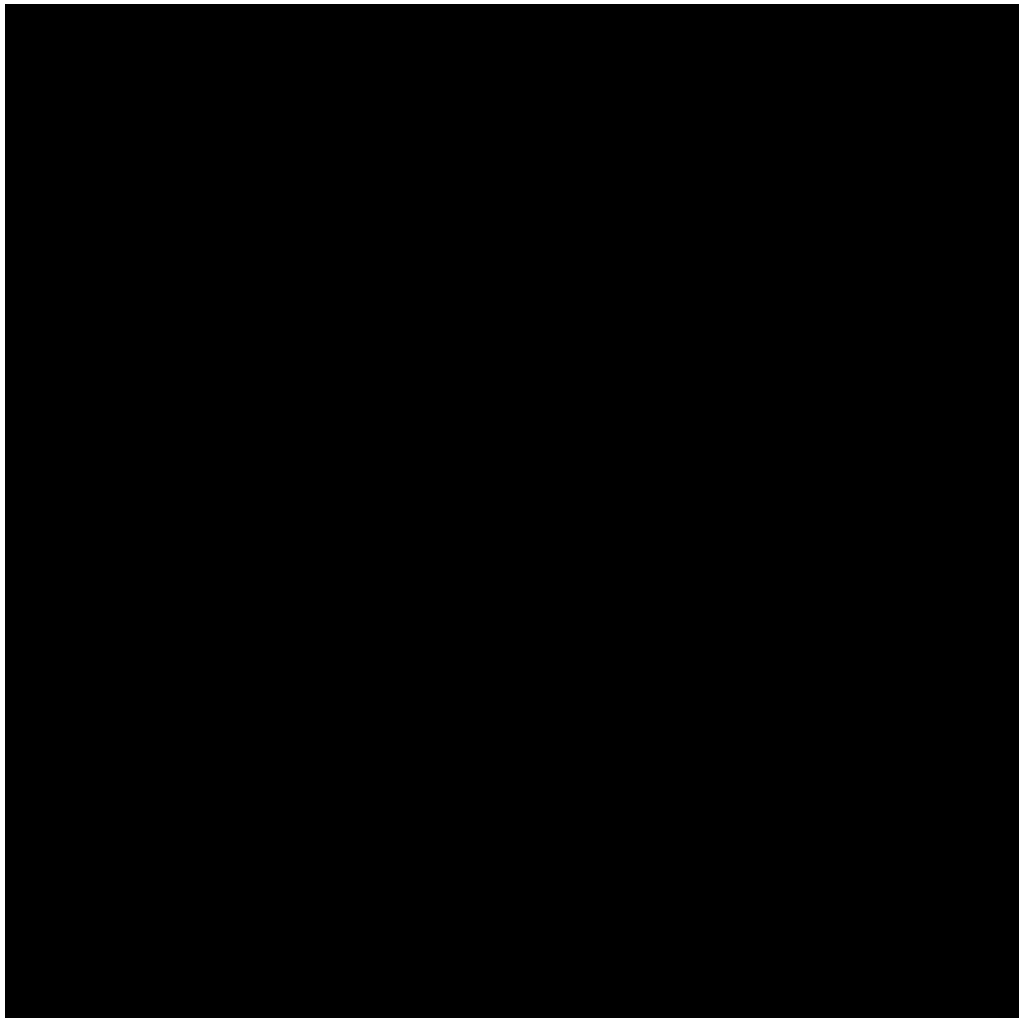
Abbreviations: C3G, complement 3 glomerulopathy; EAG, external assessment group; RaDaR, National Registry of Rare Kidney Disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Time to discontinuation

Kaplan-Meier and parametric survival analyses, pooled population



Kaplan-Meier and parametric survival analyses, APPEAR-C3G trial only population



Abbreviations: C3G, complement 3 glomerulopathy; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; gengamma, generalised gamma.

Total costs and QALYs across observed and extrapolated periods

Period	Total costs	Proportion of total costs	Total QALYs	Proportion of total QALYs
SoC				
Observed period*	£3,341	0.94%	2.12	14.01%
Extrapolate period	£351,821	99.06%	13.01	85.99%
Iptacopan + SoC				
Observed period*	[redacted]	[redacted]	1.73	10.25%
Extrapolated period	[redacted]	[redacted]	15.15	89.75%

* Observed period for is 2.5 years for SoC and 2 years for iptacopan + SoC

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

Key issue: Most QALYs & costs accrue beyond trial length

Background

- Model relied on extrapolating data beyond observed trials' length (SoC = 2.5 years, iptacopan = 2 years)
- EAG concerned that iptacopan + SoC arm accrues proportionately more QALYs and less costs in the extrapolated period than SoC alone arm

Company

- At clarification, presented total costs and QALYs by observed and extrapolated periods for each arm

EAG comments

- At clarification, requested total costs and QALYs breakdown for observed vs extrapolated periods
- Concerned by proportionately low 0.94% of total costs in SoC arm accrued during first 2.5 years (compared to [redacted] in 2 years of iptacopan) in combination with almost 90% of iptacopan QALYs from extrapolation
- Given constant treatment effect, unclear if extrapolated portion overestimates long-term incremental benefit
- Seeks explanation of model mechanism causing this difference and justification for its plausibility

See appendix for more details

Does committee require further justification or analysis regarding the modelling of costs and QALYs for the duration of the data extrapolation period?

Abbreviations: QALY, quality-adjusted life year; SoC, standard of care; EAG, external assessment group.

Key issue: Details of expert input unclear

Background

- Company informs various assumptions based on clinical and health economic expert input from advisory meetings
- Company provided a report and summaries of meetings with their submission, EAG is unclear of details

Company

- Provided a report for the advisory board on clinical interpretation of data for iptacopan in C3G
- No further written recordings of the referenced summarised meetings exist

EAG comments

- Concerned that various assumptions rely on meeting information that EAG has not seen
- Requested full minutes of advisory meetings to scrutinise assumptions

Is there sufficient detail of clinical and health economic justification provided?

Abbreviations: