National Institute for Health and Care Excellence

Health Technology Evaluation

Iptacopan for treating complement 3 glomerulopathy [ID6283]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Novartis	Novartis considers it highly appropriate for iptacopan for the treatment of complement 3 glomerulopathy (C3G) to be referred to NICE for appraisal at this time. Novartis believes that the criteria for the highly specialised technology (HST) route are met; please see the completed HST criteria checklist for further details. If the assessment is conducted using the single technology appraisal (STA) route, it should be considered that C3G is a rare disease. As acknowledged in the latest NICE health technology evaluations manual, evidence generation is challenging in rare diseases and as a result, the level of evidence for technologies indicated for rare diseases might not be as high as for other technologies.	Thank you for your comment. NICE's prioritisation board has determined that this topic will be evaluated as a single technology appraisal. No change to the scope required.

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	MPGN/DDD Support Group	Methodology of the evaluation seems reasonable.	Thank you for your comment. No change to the scope required.
	Kidney Research UK	We agree with the evaluation route proposed – highly specialised technology appraisal process	Thank you for your comment. NICE's prioritisation board has determined that this topic will be evaluated as a single technology appraisal. No change to the scope required.
	National Kidney Federation	No comment	Thank you.
	National Renal Complement Therapeutics Centre	A NICE highly specialised technology evaluation of iptacopan for C3G seems appropriate	Thank you for your comment. NICE's prioritisation board has determined that this topic will be evaluated as a single technology appraisal. No change to the scope required.
	NHS England	NICE England notes that the scope has been put forward as a Single Technology Appraisal (STA) with a question raised for consultees on the appropriateness of evaluating this topic as an HST.	Thank you for your comment. NICE's prioritisation board has determined that this topic will be evaluated as a single technology

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			appraisal. No change to the scope required.
Wording	Novartis	Novartis agrees with the wording of the remit in the draft scope	Thank you for your comment. No change to the scope required.
	MPGN/DDD Support Group	Wording in the scope is reasonable. The wording does not appropriately reflect the relevance of dialysis and other renal replacement therapies (RRT) in discussion of Iptacopan. There should be more consideration of dialysis and RRT as a comparator to Iptacopan.	Thank you for your comment. Dialysis and RRT are not considered comparators for this appraisal. No change to the scope required.
	Kidney Research UK	Yes	Thank you for your comment. No change to the scope required.
	National Kidney Federation	Yes, we are happy with this.	Thank you for your comment. No change to the scope required.
	National Renal Complement Therapeutics Centre	Yes	Thank you for your comment. No change to the scope required.
	NHS England	Yes, the remit does address the clinical issues and the cost effectiveness. The economic modelling will include the costs associated with diagnostic testing in people who would not otherwise have been tested but also should reflect the costs of centralising diagnostic services.	Thank you for your comment. No change to the scope required.

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Timing issues	Novartis	Novartis considers there is a high degree of urgency for NICE to undertake a technology appraisal in C3G. There are currently no approved targeted therapies for C3G which slow the progression of the disease. Individuals with C3G experience progressive symptom worsening alongside irreversible kidney damage, before reaching kidney failure,[2] with around 50% of patients progressing to kidney failure within 10 years of diagnosis.[3, 4] Once someone has progressed to kidney failure, they require chronic dialysis or a kidney transplant.[5, 6] Kidney transplantation is not curative, however, and there is a high rate of recurrence post-transplant (55–85%).[2, 4, 7-11] There is therefore a high unmet need in C3G. In recognition of the high unmet need and the potential of iptacopan, as the first targeted treatment addressing the underlying pathophysiology of C3G, to offer significant additional benefit, iptacopan has been awarded several regulatory designations including Priority Medicines (PRIME) designation from the European Medicines Agency (EMA).[12-14] [redacted][15] This further highlights the urgency of this evaluation for the NHS.	Thank you for your comment. This topic has been scheduled into the work programme.
	MPGN/DDD Support Group	High. Kidney Research UK released 'Kidney Disease: A UK public Health emergency' in June 2023. This document outlines the growing numbers of patients and increasing demands on dialysis services in the UK. Iptacopan has the potential to prevent C3 glomerulopathy (C3G) patients requiring dialysis, and further treatment. This would be a release of pressure on renal services in the UK.	Thank you for your comment. This topic has been scheduled into the work programme.
	Kidney Research UK	This evaluation is urgent. There are currently no NICE recommended treatments for C3 glomerulopathy so there is significant unmet need	Thank you for your comment. This topic has been scheduled

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			into the work programme.
	National Kidney Federation	The draft scope itself says there are currently no NICE recommended treatments for C3 glomerulopathy. People usually have treatment to improve kidney function, and about half of affected people develop end-stage renal disease within 10 years of their diagnosis. The only treatment for this is then dialysis or kidney transplantation to stay alive. Dialysis units are under significant pressure as an aging society, with increased rates of diabetes, high blood pressure and obesity, all increase rates of chronic kidney disease. There is currently a 2-3 year wait on average for a kidney transplant, but there is huge variation based on geography, blood type and also ethnicity. There is a high rate of recurrence of C3 glomerulopathy after a kidney transplant, so this is a cycle which may continue. Anything which can prevent patients from needing to progress to this at speed, and also relieve some of the pressure on NHS capacity and transplant waiting list is to be welcomes.	Thank you for your comment. This topic has been scheduled into the work programme.
	National Renal Complement Therapeutics Centre	There is currently no treatment for C3G and patients progress to end stage kidney failure and require dialysis. Following transplantation the disease recurs and the transplant fails. As such a treatment is urgently required.	Thank you for your comment. This topic has been scheduled into the work programme.
	NHS England	As a rare disease with no disease-specific treatments available and no other treatments expected in the near future and new patients potentially requiring treatment this evaluation should be considered as relatively urgent.	Thank you for your comment. This topic has been scheduled into the work programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novartis	Whilst Novartis considers the background section a helpful summary, we would like to suggest modifications and clarifications as outlined below. Novartis agrees that the major features of C3G are proteinuria (protein in the urine) and haematuria (blood in the urine), and other signs and symptoms may include high blood pressure, fatigue, swelling of some areas of the body (feet, hands, ankles), and reduced urine output.[6, 16-18] The draft scope currently states that dense deposit disease (DDD) may also affect tissues other than the kidneys. Novartis would like to clarify that these symptoms are not limited to patients with DDD but can occur in both subtypes of C3G, including patients with C3 glomerulonephritis (C3GN), with extrarenal symptoms of C3G encompassing acquired partial lipodystrophy, ocular drusen, and cardiovascular complications.[19] Novartis would suggest replacing the term “end-stage renal disease (ESRD)” with “kidney failure” throughout, in line with patient-preferred terminology.[20] Given the relatively recent definition of C3G as a distinct disease and its rare nature, incidence and prevalence are difficult to ascertain. The National Organization for Rare Disorders (NORD) website states an estimated prevalence of C3G of 2–3 per 1,000,000 people.[21] Further discussion of the prevalence of C3G is presented in the HST criteria checklist. Novartis would recommend reflecting the young age of patients with C3G in the background section, as an important differentiating factor from many other chronic kidney diseases. The median age at diagnosis is reported as 21–23 years old.[22, 23] Since around 50% of patients progress to kidney failure within 10 years of diagnosis,[3, 4] C3G therefore can have a significant impact on the lives of young people, and this burden should be reflected when introducing the disease.	Thank you for your comment. Please note that the background section is intended as a brief overview of the disease. The following amendments have been made to the scope: • Clarified that both subtypes of C3G can affect other tissues. • ‘ESRD’ replaced with ‘kidney failure’. • The age at diagnosis. • Risk of recurrence after transplantation. • Clarified the aim of treatment with ACEi/ARBs • Removed ‘routinely’ from eculizumab CCP discussion

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		We also think it might be helpful to quantify the high risk of C3G recurrence after kidney transplantation in the background section, with estimates in the literature ranging from 55–85%,[2, 4, 7-11] and the high risk of graft failure – requiring a return to dialysis or a further kidney transplant – among patients with disease recurrence (50–61%).[8, 9] Novartis would also ask for several updates to the text summarising current treatment strategies, to accurately describe the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and the current standard of care in the UK.[24, 25] • The draft scope states that "People usually have treatment to improve kidney function and to reduce inflammation", and subsequently mentions angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) as well as immunosuppressants. While the latter reduce inflammation, ACEi/ARBs are considered "supportive measures" only, to reduce proteinuria and manage hypertension; they do not improve kidney function.[24] • We agree that KDIGO recommends treatment with mycophenolate mofetil (MMF) plus corticosteroids in people with moderate-to-severe disease, but wish to clarify that these treatments are generally given as an add-on to ACEi/ARB (the "usual supportive measures" for all glomerular diseases).[24] Therefore, we suggest removing "initially" from the scope and adding "(in addition to ACEi/ARB)" to accurately reflect the use of these treatments. • While Novartis understands that the term "routinely commissions" accurately reflects the funding status of eculizumab for C3G, it could lead to misinterpretation around its actual level of use in UK clinical practice. Since 2017 (up to March 2023) only seven patients have qualified for treatment with eculizumab for C3G, due to the NHS England criteria restricting its use to a small subgroup among patients	

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		with post-transplant recurrence.[25-27] Novartis would therefore suggest removing “routinely” from the scope, or adding information that the use of eculizumab in UK clinical practice is very limited. Finally, Novartis would recommend that the description of the technology is adjusted. Firstly, Novartis would suggest that it is reflected that iptacopan is an oral medication. Secondly, Novartis would ask that a high-level description of the Phase 3 trial as a double-blind, randomised, placebo-controlled clinical trial is added (since information about the study design is also reflected for the non-randomised, open-label, Phase 2 study). Further, we also wish to clarify that the submission for this appraisal will include data from adult patients only.	
	MPGN/DDD Support Group	Background information provided was satisfactory.	Thank you for your comment. No change to the scope required.
	Kidney Research UK	-	Thank you.
	National Kidney Federation	No comment	Thank you for your comment. No change to the scope required.
	National Renal Complement Therapeutics Centre	The background is correct although omits describing the underlying pathogenesis- i.e. autoantibodies (C3 nephritic factors, factor H autoantibodies etc) and rare genetic variants (e.g Factor H, Hybrid genes, C3 etc). These will likely be very important for ongoing management strategies so should be covered in the background.	Thank you for your comment. The scope has been updated to clarify that C3G can have autoimmune or genetic aetiology.

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	NHS England	The NHSE commissioning position on treatment of recurrence of C3 glomerulopathy post-kidney transplant could be clearer. The policy is for adults and children according to specified criteria, notably for highly aggressive recurrent disease.	Thank you for your comment. The description of the eculizumab CCP has been updated as suggested.
Population	Novartis	The anticipated marketing authorisation for iptacopan is for the treatment of *adults* with C3G, and therefore Novartis suggest the population is adjusted in line with this.	Thank you for your comment. The scope has been updated as suggested.
	MPGN/DDD Support Group	Population is defined appropriately.	Thank you for your comment. No change to the scope required.
	Kidney Research UK	Children under the age of 12 years are excluded from the population. We understand this is because of the status of clinical trials but is there an opportunity to make approvals contingent upon the delivery of trials in younger children?	Thank you for your comment. The committee will assess the evidence presented to it and evaluate iptacopan within the marketing authorisation population specified by the MHRA. No change to the scope required.
	National Kidney Federation	Yes	Thank you for your comment. No change to the scope required.

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	National Renal Complement Therapeutics Centre	Yes	Thank you for your comment. No change to the scope required.
	NHS England	Support an all-ages review which seems to be in line with the scope and reflects the lifetime burden of disease in children.	Thank you for your comment. The committee will assess the evidence presented to it and evaluate iptacopan within the marketing authorisation population specified by the MHRA. No change to the scope required.
Subgroups	Novartis	Due to the rarity of C3G and therefore small sample sizes in clinical trials, Novartis considers that subgroup analyses are not likely to provide meaningful results. While the iptacopan clinical trial programme in C3G included both patients with native kidney disease and patients with post-transplant disease recurrence, subgroup analyses for people who have and have not had a kidney transplant were not requested in recent NICE appraisals of another glomerular disease or chronic kidney disease.[28-31] When diagnosing C3G, a distinction can be made between C3GN and DDD according to kidney tissue biopsy findings at the electron microscopy level.[32, 33] However, the clinical presentation, disease course and management of these C3G subtypes are generally considered to be consistent.[2-4, 34] Given the similarity, Novartis would not expect clinical and cost effectiveness of iptacopan to differ between C3GN and DDD. Analysing these subgroups	Thank you for your comment. The committee will determine relevant subgroups based on the available evidence. No change to the scope required.

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		would also break study randomisation, therefore introducing further uncertainty for decision-making. We therefore suggest these subgroups are removed.	
	MPGN/DDD Support Group	Clinician advice should be taken in comparing C3GN and DDD patients. Other subgroups are satisfactory.	Thank you for your comment. No change to the scope required.
	Kidney Research UK	The subgroups listed in the scope are appropriate – C3G is sub-divided into people with C3 glomerulonephritis and people with dense deposit disease	Thank you for your comment. No change to the scope required.
	National Kidney Federation	No comment	Thank you.
	National Renal Complement Therapeutics Centre	CFHR5 nephropathy is not included in the subgroups and should be specifically considered	Thank you for your comment. This subgroup has been added to the scope.
	NHS England	The subgroups are appropriate.	Thank you for your comment. No change to the scope required.
Comparators	Novartis	Novartis agrees that the “established clinical management” comparator reflects current standard of care in the NHS. Given the design of the iptacopan clinical trials and the expected indication wording, we would suggest that the text could be reworded to “Established clinical management without iptacopan, such as angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARBs) at the maximum tolerated licensed doses, with or without:	Thank you for your comment. SGLT2 inhibitors have been added to the comparator list. The committee will determine the appropriate

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		○ Corticosteroids ○ Mycophenolate mofetil” Sodium-glucose co-transporter-2 (SGLT2) inhibitors may also increasingly be used as part of established clinical management, as supportive background medication alongside ACEi/ARB, although no data for C3G exists and clinical uptake in the UK may currently be limited. Considering the post-transplant recurrent population, eculizumab use is uncommon in UK clinical practice as outlined in our comments to the “Background information” section above,[25, 26] with the criteria of the NHS England commissioning policy restricting its use to a small subgroup among patients with post-transplant recurrence (requiring e.g. presence of active glomerulonephritis with cellular crescents, evidence of glomerular C9 deposition, and >20% decline in estimated glomerular filtration rate [eGFR] within the previous three months).[27] Therefore, the use of eculizumab may not be considered sufficient to amount to established practice in the NHS.	comparators based on the available evidence.
	MPGN/DDD Support Group	No. The comparators listed are reasonable and valid. However, RRT in the form of dialysis in each of its modalities, and transplantation are not listed as comparators. It has been established that ~50% of C3G patients will reach ESRD in 10 years and require RRT so it should be considered as treatment. Without RRT in ESRD, C3G patients would die. Comparators should therefore include: In-Centre Haemodialysis Home Haemodialysis Peritoneal Dialysis Deceased Donor Transplantation Directed Living Donor Transplantation	Thank you for your comment. If approved, iptacopan would not replace dialysis, so dialysis cannot be considered as a comparator. However, it is anticipated that the need for dialysis/transplantation will be considered under the outcome ‘disease progression’

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		UKLKSS Donor Transplantation Altruistic Donor Transplantation All associated costs of these treatments should be considered. All impacts on patients' health and quality of life should be considered.	No change to the scope required.
	Kidney Research UK	All commonly used comparators are included. In paediatric practice, rapidly progressive disease might be treated with other treatments including IV cyclophosphamide, rituximab and plasma exchange but this is an infrequent scenario.	Thank you for your comment. Please note the company comment above that this submission will be for adults only. No change to the scope required.
	National Kidney Federation	No comment	Thank you.
	National Renal Complement Therapeutics Centre	The comparators include the KDIGO recommended treatments. Eculizumab is included for transplantation in line with NHSE policy.	Thank you for your comment. No change to the scope required.
	NHS England	The comparators are appropriate. In post-transplant for eculizumab only a sub-set of patients meet criteria therefore most post-transplant patients have no additional comparator.	Thank you for your comment. No change to the scope required.
Outcomes	Novartis	The listed outcomes are generally appropriate, but Novartis would suggest rewording for consistency with the final scope of treatments for other glomerular diseases, as well as accuracy.[28, 29] We would consider the following list of outcomes as the most appropriate for this appraisal:	Thank you for your comment. The outcomes list has been updated as suggested.

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		• Proteinuria (for example, change from baseline in urine protein creatinine ratio [UPCR]) • Kidney function (eGFR) • Disease progression (dialysis and/or transplant) • Mortality • Adverse effects of treatment • Health-related quality of life While proteinuria is a key outcome, Novartis disagrees with its current listing as a measure of kidney function. Whilst the draft scope lists “need for kidney transplant” as an outcome measure, kidney failure results in the need for either dialysis or a transplant, and we suggest listing these jointly under “disease progression”. The above proposal fully aligns with the final scope of previous/ongoing appraisals for the treatment of immunoglobulin A (IgA) nephropathy,[28, 29] another glomerular disease.	
	MPGN/DDD Support Group	All outcomes listed are suitable.	Thank you for your comment. No change to the scope required.
	Kidney Research UK	We think that the outcomes are appropriate.	Thank you for your comment. No change to the scope required.
	National Kidney Federation	Quality of life is an essential measure for patients with C3 glomerulopathy- as many of the current treatment options are high burden and incredibly invasive. Both dialysis and transplantation, even if successful, take their toll on the person with kidney disease and their family.	Thank you for your comment. No change to the scope required.

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	National Renal Complement Therapeutics Centre	C3G is a chronic condition that progresses over years and as the kidney does not regenerate any improvement in eGFR is likely to be slight. Instead you are looking to prevent deterioration in function. A more appropriate measure of efficacy would be stabilisation of deterioration in renal function vs a comparator group.	Thank you for your comment. The outcome has been updated to reflect this.
	NHS England	The outcomes are appropriate.	Thank you for your comment. No change to the scope required.
Equality	Novartis	Novartis supports access to treatment for all people with C3G regardless of their age, disease severity and socioeconomic background. Equality of access is a key consideration for Novartis, and we are committed to supporting the availability of iptacopan to all eligible patients in England and Wales.	Thank you for your comment. No change to the scope required.
	MPGN/DDD Support Group	There is no changes necessary on the grounds of equality.	Thank you for your comment. No change to the scope required.
	Kidney Research UK	Children under the age of 12 years are excluded and thus are discriminated against. We understand this is because of the status of clinical trials but is there an opportunity to make approvals contingent upon the delivery of trials in younger children?	Thank you for your comment. The committee will assess the evidence presented to it and evaluate iptacopan within the marketing authorisation population specified by

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			the MHRA. No change to the scope required.
	National Kidney Federation	• It should be kept in mind that there is a longer waiting time for kidney transplants for black and Asian patients compared to white. 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 were Asian, 1 per cent were black and 2 per cent were mixed race. • This may need to be factored in when considering who should be treated and when, to ensure all patients have the best chance.	Thank you for your comment. The Equality Impact Assessment has been updated to reflect this.
	National Renal Complement Therapeutics Centre	The draft remit & scope is appropriate from an equality point of view	Thank you for your comment. No change to the scope required.
	NHS England	Access for children and adolescents needs to be considered in scope. No other comments.	Thank you for your comment. The committee will assess the evidence presented to it and evaluate iptacopan within the marketing authorisation population specified by the MHRA. No change to the scope required.
Other considerations	Novartis	A kidney biopsy is required to diagnose C3G and to differentiate the disease from other forms of glomerulonephritis which often present with similar symptoms, such as IgA nephropathy.[23, 24, 33] This diagnostic biopsy ensures	Thank you for your comment. The economic modelling

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		that the patient receives an accurate diagnosis and optimal clinical management. In line with the design of the clinical trials and the anticipated licence wording, iptacopan is intended as an add-on to established clinical management (ACEi/ARB), and not as a first-line treatment for C3G. Therefore, the cost of diagnostic testing should not be included in the cost-effectiveness modelling of iptacopan. This aligns with NICE appraisals in IgA nephropathy, another glomerular disease which requires a kidney biopsy for diagnosis, and where the interventions under assessment are positioned after ACEi/ARB.[28, 29]	should include the costs associated with diagnostic testing in people who would not otherwise have been tested. No change to the scope required.
	MPGN/DDD Support Group	-	Thank you.
	Kidney Research UK	-	Thank you.
	National Kidney Federation	No comment	Thank you.
	National Renal Complement Therapeutics Centre	Given the likely cost of iptacopan consideration should be given diagnostics provision- e.g. pronase digestion of biopsies, immunofluorescence for pathology, staining for kappa and lambda light chains, detection of underlying genetic abnormalities and the presence of nephritic factors, complement autoantibodies and complement analytes. These will likely personalise management once in clinical use. Not all pathology centres will have access to immunofluorescence, kappa and lambda light chain staining and pronase digestion. Genetic and complement autoantibody testing is available nationally.	Thank you for your comment. The economic modelling should include the costs associated with diagnostic testing in people who would not otherwise have been

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			tested. No change to the scope required.
	NHS England	The economic modelling is to include testing for patients who would not otherwise be tested. The costs need to be considered of setting up a national diagnostic service for all patients recognising variation in renal pathology. Current costs won't be released from the system.	Thank you for your comment. The economic modelling should include the costs associated with diagnostic testing in people who would not otherwise have been tested. No change to the scope required.
Questions for consultation	Novartis	*Are all relevant comparators included? Would iptacopan be used alongside or instead of ACE inhibitors, ARBs, corticosteroids and mycophenolate mofetil?* Please refer to the "Comparators" section above. Iptacopan would be used in combination with an ACEi or ARB, in line with the design of the clinical trials and the anticipated indication wording. Iptacopan can also be used in combination with corticosteroids and/or MMF. The Phase 3 trial included patients with a urine protein to creatinine ratio (UPCR) of ≥1.0 g/g despite treatment with a maximally recommended or tolerated dose of an ACEi or ARB.[5] Patients on a stable dose of corticosteroids or MMF were also eligible for enrolment, with all medications maintained on a stable dose during the trial.[5] It is expected that iptacopan would be used in UK clinical practice in a similar way. *Is eculizumab ever used in the NHS for people with C3 glomerulopathy who have not previously had a kidney transplant?*	Thank you for your comment. No change to the scope required.

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		The NHS England commissioning policy restricts the use of eculizumab for C3G to a small subgroup among patients with post-transplant recurrence of C3G.[27] Based on conversations with UK clinicians, we understand that these criteria are adhered to in clinical practice.[25] Even in patients with post-transplant recurrence, eculizumab is rarely used in the UK, with only seven patients meeting the criteria for treatment between February 2017 and March 2023.[26] *How is moderate-to-severe C3 glomerulopathy defined in clinical practice?* UK clinical experts advise that they align clinical management to the international KDIGO guidelines which define moderate to severe disease as proteinuria >1g/day and haematuria or declining kidney function for at least 6 months.[24, 25] Corresponding with this, the iptacopan Phase 3 trial included patients with UPCR of ≥1.0 g/g despite treatment with a maximally recommended or tolerated dose of an ACEi or ARB.[5] *Does diagnosis of C3 glomerulopathy in order to be eligible for iptacopan require biopsy or other diagnostic testing in people that would otherwise not have been tested?* A kidney biopsy is required to diagnose C3G and to differentiate the disease from other forms of glomerulonephritis which often present with similar symptoms, such as IgA nephropathy.[23, 24, 33] Please refer to the "Other considerations" section above for further details. It is expected that clinicians will determine a patient's current eGFR and UPCR levels while considering suitability for treatment with iptacopan; however, these measures are part of routine monitoring for all C3G patients regardless of treatment.	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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		Where do you consider iptacopan will fit into the existing care pathway for C3 glomerulopathy? We expect that iptacopan would be used in adult C3G patients who are at high risk of progressing to kidney failure despite treatment with current standard of care. In the Phase 3 study of iptacopan, which included patients who had not previously had a transplant (native kidney C3G), this was defined as UPCR of ≥1.0 g/g despite treatment with a maximally recommended or tolerated dose of an ACEi or ARB.[5] Some patients may also be on corticosteroids and/or MMF when being considered for iptacopan treatment, although use of these treatments in UK clinical practice varies, with careful consideration of the patient's presentation (e.g. inflammatory activity on kidney biopsy) and the treatment risk/benefit profiles, and enrolment in clinical trials is currently often preferred over use of these treatments.[25] In addition to patients with native kidney C3G and high risk of disease progression, we would also anticipate use of iptacopan in patients with recurrence of C3G following a kidney transplant. For this positioning, evidence is available from the Phase 2 study of iptacopan.[35] *Please select from the following, will iptacopan be:* *A. Prescribed in secondary care with routine follow-up in primary care* *B. Prescribed in secondary care with routine follow-up in secondary care* *C. Other (please give details):* *For comparators please detail if the setting for prescribing and routine follow-up differs from the intervention.* Iptacopan is expected to be prescribed in secondary care with routine follow-up in secondary care (Option B).	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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		While ACEis and ARBs can also be prescribed in primary care, we assume that patients who would be considered for treatment with iptacopan (see response to previous question) are already routinely followed up in secondary care. *Are the subgroups listed appropriate?* Please refer to the "Subgroups" section above. *Are the outcomes listed appropriate? Is it anticipated that iptacopan would be effective in reducing non-renal symptoms in dense deposit disease? If so, are there any further outcomes which should be considered?* Please refer to the "Outcomes" section above, which we believe captures the key outcomes relevant for C3G. As noted above, non-renal symptoms and complications, including cardiovascular disease, are not specific to DDD but occur in C3G more broadly.[2-4, 34] The efficacy of iptacopan on non-renal outcomes has not been investigated within the clinical trials. *Would iptacopan be a candidate for managed access?* At time of submission, approximately three years of iptacopan follow-up data will be available from patients who entered a long-term extension study following completion of the Phase 2 study. Notwithstanding the typical challenges observed for evidence generation in rare diseases, Novartis believes that the evidence available at time of the NICE appraisal will be sufficient for the committee to evaluate the use of iptacopan in routine clinical practice.	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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		Do you consider that the use of iptacopan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? While the main benefit of iptacopan in slowing decline in kidney function will be captured in the economic modelling, not all benefits are likely to be fully reflected in the QALY calculation. Fatigue is a common symptom in C3G and associated with high patient burden.[16, 36, 37] However, standard generic health-related quality of life (HRQoL) instruments utilised for generating health state utility values for economic modelling may not be able to capture the full impact of fatigue on patients' HRQoL. In particular, the EQ-5D has been shown to have low sensitivity to the impact of fatigue on HRQoL.[38] Consequently, benefits of iptacopan in terms of reducing fatigue may not be fully captured in QALYs based on health state utility values generated from a generic HRQoL instrument. C3G has a large impact on patient and carer quality of life, which is not fully captured in modelling QALYs and costs from an NHS perspective. People receiving dialysis require multiple sessions per week, with sessions taking multiple hours.[39] Individuals with C3G, as well as carers, may therefore have to reduce hours at work or in education as a result of their disease.[6, 40] *NICE is considering evaluating this technology through its Highly Specialised Technologies Evaluation Programme. We welcome comments on the appropriateness of evaluating this topic through this process.* Novartis considers the HST route the most appropriate process for the appraisal of iptacopan for C3G and believes that the criteria are met; please see the completed HST criteria checklist for further details.	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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	MPGN/DDD Support Group	- *Are all relevant comparators included? Would Iptacopan be used alongside or instead of ACE inhibitors, ARBs, corticosteroids and mycophenolate mofetil?* Iptacopan would be used instead of MMF and Corticosteroids. Iptacopan may be used alongside ACEi and ARBs to control symptoms that may have resulted from prior disease damage or underlying hypertension to prevent other renal damage from progressing. This treatment would be at the discretion of the Nephrologist RRT should be considered as stated above. - *Is eculizumab ever used in the NHS for people with C3 glomerulopathy (C3G) who have not previously had a kidney transplant?* This question should be answered by NHS clinicians. - *How is moderate-to-severe C3G defined in clinical practice?* It is defined by the rate of deterioration of kidney function. Therefore, moderate to severe C3G is defined as: Moderate – stably declining renal function Severe – rapidly declining renal function Renal function is measured by numerous methodologies including blood and urine testing. Significant indicators include Creatinine, eGFR and Proteinuria - *Does diagnosis of C3 glomerulopathy in order to be eligible for Iptacopan require biopsy or other diagnostic testing in people that would otherwise not have been tested?*	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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		No. Iptacopan would only be indicated for the cohort that have been diagnosed by biopsy due to investigation being necessary as a result of their declining kidney function, whether symptomatic or due to incidental findings. The timing of biopsy is at the discretion of the treating Nephrologist. - *Where do you consider Iptacopan will fit into the existing care pathway for C3 glomerulopathy?* *Please select from the following, will Iptacopan be:* *A. Prescribed in secondary care with routine follow-up in primary care* *B. Prescribed in secondary care with routine follow-up in secondary care* *C. Other (please give details):* *For comparators please detail if the setting for prescribing and routine follow-up differs from the intervention.* Iptacopan should be prescribed in 2° care and followed up in 2° care. Any treatments for C3G should be overseen by 2° care clinicians. - *Are the outcomes listed appropriate? Is it anticipated that Iptacopan would be effective in reducing non-renal symptoms in dense deposit disease? If so, are there any further outcomes which should be considered?* There are many health-related complications from living with ESRD and having dialysis treatment. In this sense, the use of Iptacopan could reduce the need for dialysis and hence reduce these other non-renal symptoms. Heart health is compromised. For example, we know of a nineteen-year-old DDD patient who had a cardiac arrest whilst having his dialysis treatment. This resulted in a prolonged stay on the high dependency cardiac ward.	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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		During the admission in hospital he became ill with sepsis. It is very common for C3G patients receiving RRT to have multiple hospital admissions for renal related health complications. DDD patients, in common with other kidney patients on dialysis, often have low haemoglobin levels that are difficult to stabilise. Low haemoglobin results in severe tiredness and can necessitate the need for blood transfusions. Having blood transfusions often limits the pool of donors that a patient waiting for a transplant can receive a kidney from. This results in being on dialysis for longer and a declining state of health. - *Do you consider that the use of Iptacopan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.* <u>Health Benefits</u> Health benefits are gained by stopping the disease before patients decline into ESRD, when they will require dialysis, or a transplant, to stay alive. 1. This will avoid the need to be on immunosuppressants for life, following a kidney transplant. This means a reduced risk of developing other diseases. 2. Improved growth in children. Children on dialysis do not grow as well as other children. Reduces the need for children to be on growth hormones. 3. Improved bone health meaning less pain in the bones and joints. Increased ability to exercise as the bones will be stronger. Calcium levels in the bones can be reduced when on dialysis.	Thank you for your comment. No change to the scope required.

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		4. Having a normal HB level would give patients a greater capacity to work, exercise, and engage in life. Low HB levels mean that patients are severely anaemic and struggle to maintain a good quality of life. 5. Appropriate HB levels would remove the need for blood transfusions. Blood transfusions reduce a patient's pool of donors and results in a longer wait for a transplant. 6. Reduced risk of death from suicide. Dialysis patients are at a greater risk of suicide than non-dialysis cohorts. 7. Improved quality of life for patients. The ability to lead a normal life, rather than fit a life around dialysis treatment. For dialysis patients receiving in centre treatment, it often takes out three days a week of normal life. With a four hour treatment time on a machine, plus waiting to get set up on a machine and taken off a machine, plus transport time to and from a centre, it can take up most of the day. Tiredness after treatment means that effectively patients lose three days a week and can only live a normal life for the remaining four days a week. 8. Improve the mental health of patients by offering an alternative future to the cycle of dialysis/transplant/dialysis. 9. Improving life expectancy. Life expectancy for dialysis patients is five years.	
	Kidney Research UK	Answering the consultation questions in sequence: It is likely that iptacopan will be used alongside ACEi and ARB, which have benefits regardless of the cause of proteinuria. If iptacopan is approved, we expect clinicians will commence iptacopan in existing patients in order to reduce and then stop their existing immunosuppression with steroids +/- MMF. In newly presenting patients with mild to moderate disease, we expect that iptacopan could replace steroids/MMF completely. In patients with newly presenting severe disease, we anticipate that steroids may be necessary	Thank you for your comment. No change to the scope required.

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		initially in order to reduce severe inflammation. However we would anticipate this would be of short duration only (e.g. < 3 months) and that MMF may not be needed in most patients who are treated with iptacopan. Eculizumab is used extremely rarely in the NHS for people with C3 glomerulopathy who have not previously had a kidney transplant. Moderate C3G would be defined by nephrotic range proteinuria and/or impaired kidney function. Severe C3G would be defined by an acute, progressive decline in kidney function (almost always accompanied by nephrotic range proteinuria). A diagnosis of C3G can only be made by a kidney biopsy and therefore a biopsy is required regardless of available treatments. we think prescribing of iptacopan could be within secondary care (adults) or tertiary care (paediatrics), with oversight/shared care from a highly specialised service, similar to eculizumab for aHUS. Benefits of centralised oversight would include equitable access to accurate diagnostics in order to initiate treatment, and expedited learning regarding the best real-world use of iptacopan. For example understanding which particular diagnostic/monitoring biomarkers correlate with response to treatment, where iptacopan fits into the overall treatment pathway, when treatment can be discontinued and adverse effect surveillance. For comparators, the setting for prescribing and routine follow-up is as follows:	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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		Adults: current care pathways are typically prescribed in secondary care, with routine follow up in secondary care. Prescribing may be undertaken by primary care under supervision – practice varies. Children: current care pathways are typically initiated in tertiary care, with routine follow up in shared care between tertiary and secondary care. Prescribing may be undertaken by primary care under supervision – practice varies. We think iptacopan would be ideally suited to managed access. In terms of whether iptacopan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation, ESRD has a massive impact on non-health outcomes such as ability to work. The wider impact of a child developing ESRD – parental employment and mental health, impact on siblings (mental health) and future employment also should be considered. If iptacopan can stop/delay development of ESRD, these are significant benefits which should be explored. For children, PedQL can be used to capture quality of life data that includes School functioning. Stories from patients and families with lived experience should be included in the outcome assessment to capture these unmeasured potential benefits. Some helpful references: The significance of relationships and dynamics in families with a child with end-stage kidney disease: A qualitative study - PubMed (nih.gov) Experiences of parents who have children with chronic kidney disease: a systematic review of qualitative studies - PubMed (nih.gov)	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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	National Kidney Federation	No comment	Thank you.
	National Renal Complement Therapeutics Centre	-	Thank you.
	NHS England	NICE England notes that the scope has been put forward as a Single Technology Appraisal (STA) with a question raised for consultees on the appropriateness of evaluating this topic as an HST. Eculizumab is not commissioned in the NHS for use in patients who have not previously had a kidney transplant. It is expected that the management of C3G will be centralised with a national expert centre will have oversight of the management of patients with C3G and the prescribing of iptacopan. A formal diagnostic pathway would be commissioned. Prescribing and day to day patient management would take place in collaboration with the expert centre in secondary care services, specialised renal centres in line with comparators. This approach will help ensure equity of diagnosis and treatment uptake and improve patient selection through clinical experience.	Thank you for your comment. No change to the scope required.
Additional comments on the draft scope	Novartis	No further comments.	Thank you.
	MPGN/DDD Support Group	IMPROVEMENTS TO QUALITY OF LIFE Having a treatment that targets C3G and prevents patients from reaching ESRD has the potential to radically improve the quality of life for patients, and	Thank you for your comment. No change to the scope required.

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		their families. We have already highlighted health gains, but patients, and caregivers, would benefit in other areas of life. Diet Many patients on dialysis are on a fluid restriction and have to follow a renal diet. The renal diet requires patients to reduce their intake of sodium, potassium, and phosphate. These restrictions make it very difficult for C3G patients to socialise with friends and family, as many social activities take place around eating and drinking. This can lead to social isolation. A treatment for C3G that stops disease progression to ESRD would improve the quality of life of patients by making it easier to join in with socialising around eating and drinking. Travel For C3G patients on dialysis, travel cannot be spontaneous. This restricts the events that patients might like to attend, and makes holidays difficult. For peritoneal dialysis patients going on holiday, it means taking a large, heavy machine, and lots of ancillary equipment. It requires space to set up the machine and space to store the ancillary equipment, plus lots of boxes of fluid. Arrangements can be made for the boxes of fluid to be delivered to a holiday destination, but the boxes need to be stored once they have arrived. The whole process can be stressful, because there is so much to take and there is a lot at stake if anything is forgotten. This is on top of medication that needs to be packed for the trip. For in centre C3G haemodialysis patients wanting to go on holiday, arrangements can be made for dialysis treatment to take place in another centre. However, this can involve anxiety around having different staff	

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		needling the fistula. Also, it will involve extra tests beforehand and on return to the regular dialysis centre, to mitigate the spread of infection. A treatment for C3G that has the potential to stop disease progressing to ESRD, would allow patients the freedom to travel and attend events more easily. It would open up many opportunities and the option to be spontaneous about social plans. Caregivers and Families When a child is diagnosed with C3G and requires a lot of treatment and care in hospital, it affects the whole family. This is especially impactful when that child progresses to ESRD and requires RRT. Siblings will face disruption to their lives. This might be when one of their parents is absent with the C3G patient during a hospital admission. It could be waking up at night when a peritoneal dialysis machine is alarming. It might mean spending several days a week at a hospital during the school holidays, whilst the child with C3G is having in centre dialysis. The parent taking the C3G patient to hospital, will often be the one to look after the other children during the holidays. The whole uncertainty that comes with having a sibling with a rare, debilitating disease, can be a cause of deep worry for children. Medication Burden For patients with C3G, there is currently a considerable medication burden. At present there is not an available targeted treatment, so patients are given different combinations of drugs to attempt to mitigate the effects of the disease on their bodies and to attempt to slow down disease progression – often unsuccessfully. For those C3G patients who have progressed to ESRD, they may have developed other co morbidities, that require medication. The management of medication, such as trips to the pharmacy, chasing up	

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		prescriptions etc. can become burdensome. Also, the sheer number of required medications, and their timings around food can take a toll on patients. For some patients, certain medications must be taken with food, other medications must not be taken with food and other tablets need to be taken a certain number of hours apart. There is a lot to manage and remember. Having a targeted treatment for C3G, taking just one pill that stops C3G in its tracks, has the potential to render other current medications unnecessary. ECONOMIC CONSIDERATIONS There doesn't seem to be a wider appreciation of the economic saving that would result from a treatment that could stop C3G patients reaching ESRD and a life dependent on RRT. Not all patients are suitable to be put forward for transplantation. Others will wait years for a suitable kidney to become available. There is increasing demand on dialysis centres across the NHS, with most centres already at capacity. A treatment that would stop C3G progressing to ESRD would ease the demand on dialysis centres. Patients cannot always get into their local centre and end up travelling much further afield for treatment. Many patients on dialysis are too unwell to work, or struggle to find employment that will fit around the three times a week treatment. It is especially difficult for young adults, who have transitioned into adult services, to embark on employment. For C3G patients diagnosed as adults, with an established career and understanding employers, accommodations are more likely to be explored. Government ministers often talk about the 'economically	

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		inactive' but many people living with chronic diseases such as C3G would like the opportunity to live a normal life and to have the ability to work. A life free from the need of dialysis would make this much more likely. For children with C3G, who have progressed to ESRD and require dialysis, there is an economic price paid by their caregivers. Children under the age of sixteen require a chaperone in the hospital transport. The younger the child at ESRD, the greater number of days of dialysis that will be required. Sometimes this could be four or five times a week. It is practically impossible for the parent of a young child with C3G to maintain a career. There can be hospital admissions for three weeks at a time, which will necessitate a parent staying with their child. For the parent who gives up a career, it means a lack of income, increased costs (food in hospital etc.) and the inability to contribute to a pension. There are welfare benefits that can help, but it is unlikely to compensate for the loss of income that they would have had. Transport costs for dialysis patients are huge. Just one return trip for a child travelling for dialysis treatment can cost around £400. This is because there are fewer dialysis centres for children, and they might have to travel three hours for treatment. The drivers will stay all day and then drive the patient home. So, that could easily amount to around £5000 a month for just one patient.	
	Kidney Research UK	-	Thank you.
	National Kidney Federation	No comment	Thank you.

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	National Renal Complement Therapeutics Centre	Any additional comments on the draft scope 1. Iptacopan should be used alongside ACE inhibitors / ARBs but should be used instead of corticosteroids and mycophenolate mofetil. Given the anecdotal & retrospective data for steroids and MMF (cf. the phase 3 randomised controlled trial of iptacopan) steroids & MMF should be third line treatment. 2. Eculizumab is not used in the NHS for people with C3 glomerulopathy who have not previously had a kidney transplant due to the lack of controlled data available. 3. Moderate disease would be defined as Urine protein over 500 mg/24 h despite supportive therapy; or moderate inflammation on renal biopsy; or recent increase in serum creatinine suggesting risk for progressive disease 4. Severe disease would be defined as: urine protein over 2000 mg/24 h despite immunosuppression and supportive therapy; severe inflammation represented by marked endo- or extracapillary proliferation with or without crescent formation despite immunosuppression and supportive therapy; or increased serum creatinine suggesting risk for progressive disease at onset despite immunosuppression and supportive therapy 5. The diagnosis of C3 glomerulopathy does require a renal biopsy and other tests such as pronase digestion of biopsies, immunofluorescence for pathology, staining for kappa and lambda light chains which are only available in certain specialist centres. Detection of underlying genetic abnormalities and the presence of nephritic factors, complement	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.

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		autoantibodies and complement analytes will also be required and these are only available in highly specialist centres 6. Iptacopan should be used after optimisation of ACEi/ARB and before MMF and steroids The evidence for iptacopan is presented in a randomised double blind controlled trial. The evidence for MMF and steroids is anecdotal and retrospective. 7. Iptacopan should be prescribed in highly specialised centres and followed up in specialist centres. 8. Iptacopan should be a candidate for managed access 9. Phase 2 and phase 3 studies are available documenting iptacopan's efficacy in C3G	Thank you for your comment. No change to the scope required. Thank you for your comment. No change to the scope required.
	NHS England	-	Thank you.