

Oral iptacopan therapy in patients with C3 glomerulopathy: a randomised, double-blind, parallel group, multicentre, placebo-controlled, phase 3 study



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Summary

Background C3 glomerulopathy is an ultra-rare, severe form of glomerulonephritis caused by overactivation of the alternative complement pathway. We aimed to assess efficacy and safety of iptacopan (LNP023), an oral, proximal complement inhibitor that targets factor B to selectively inhibit the alternative pathway of the complement cascade.

Methods APPEAR-C3G was a multicentre, randomised, double-blind, placebo-controlled, phase 3 study of iptacopan versus placebo (both in addition to supportive care [renin–angiotensin–aldosterone system (RAAS) inhibitors] and immunosuppression). Adult participants (aged 18–60 years) with biopsy-confirmed C3 glomerulopathy were enrolled from 35 hospitals or medical centres in 18 countries. Inclusion criteria included reduced serum C3 concentration (ie, <77 mg/dL [defined as <0.85×lower limit of the central laboratory normal range]) at screening, urine protein–creatinine ratio (UPCR) of 1.0 g/g or higher at day –75 and day –15 before randomisation, estimated glomerular filtration rate (eGFR) of 30 mL/min per 1.73 m² or higher at screening and day –15, and vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae*. All eligible participants were randomised 1:1 via interactive response technology to either the iptacopan or the placebo group, stratified by treatment with corticosteroids, mycophenolic acid, or both (yes or no). During the 6-month double-blind period, participants orally received either iptacopan 200 mg twice daily or placebo; this was followed by a 6-month open-label period in which all participants received iptacopan 200 mg twice daily. The primary endpoint was relative reduction in proteinuria (measured by log-transformed ratio to baseline in UPCR sampled from a 24-h urine collection) at 6 months. The primary analyses were done in the full analysis set (ie, all participants to whom study treatment was assigned by randomisation); all participants who received at least one dose of study treatment were included in the safety analysis. This trial was registered with ClinicalTrials.gov (NCT04817618) and the adult cohort has been completed.

Findings Between July 28, 2021, and Feb 15, 2023, 132 participants were screened, of whom 58 did not complete the screening period and 74 (64% male; 69% White) were randomised 1:1 to receive either iptacopan (n=38) or placebo (n=36). One participant in the placebo group discontinued treatment during the open-label period. The 24-h UPCR percentage change relative to baseline at 6 months was –30.2% (95% CI –42.8 to –14.8) in the iptacopan group and 7.6% (–11.9 to 31.3) in the placebo group. In the iptacopan group, the geometric mean of 24-h UPCR was 3.33 g/g (95% CI 2.79 to 3.97) at baseline and 2.17 g/g (1.62 to 2.91) at 6 months; in the placebo group, this was 2.58 g/g (2.18 to 3.05) at baseline and 2.80 g/g (2.37 to 3.30) at 6 months. The primary endpoint was met with a relative reduction in 24-h UPCR at 6 months for iptacopan versus placebo of 35.1% (13.8 to 51.1; p=0.0014). 30 (79%) of 38 participants in the iptacopan group had treatment-emergent adverse events, compared with 24 (67%) of 36 participants in the placebo group; most of these were of mild or moderate severity. There were no deaths, no treatment discontinuations due to treatment-emergent adverse events, and no meningococcal infections. Serious adverse events were reported in three (8%) participants in the iptacopan group and one (3%) participant in the placebo group.

Interpretation Iptacopan showed a statistically significant, clinically meaningful proteinuria reduction in addition to RAAS inhibitors and immunosuppression at 6 months. Iptacopan was well tolerated with an acceptable safety profile in patients with C3 glomerulopathy.

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Introduction

C3 glomerulopathy is an ultra-rare and severe form of primary chronic glomerulonephritis with an estimated

global incidence of 1–2 new cases per million individuals per year, which predominantly affects patients younger than 40 years.¹ C3 glomerulopathy has a highly

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See Online for appendix

Research in context

Evidence before this study

C3 glomerulopathy is an ultra-rare, progressive kidney disease that is caused by overactivation of the complement alternative pathway. There were no targeted treatments before iptacopan (LNP023), which was approved for the treatment of adult patients with C3 glomerulopathy by both the US Food and Drug Administration and the European Medicines Agency in 2025. Current guideline recommendations rely on supportive care (ie, blockade of the renin–angiotensin–aldosterone system with angiotensin-converting enzyme inhibitors or AT1 receptor blockers) with or without immunosuppression (eg, mycophenolic mofetil or corticosteroids), which has limited benefits and often considerable side-effects. Iptacopan is an oral complement inhibitor that targets factor B and selectively inhibits the alternative pathway by blocking C3 convertase activity and inhibiting the alternative pathway amplification loop, thus preventing downstream generation of alternative pathway C5 convertase, C3a and C5a anaphylatoxins, and the membrane attack complex. Iptacopan is also approved for the treatment of adults with paroxysmal nocturnal haemoglobinuria and for the reduction of proteinuria in adults with primary IgA nephropathy. In a phase 2 study, 12-week iptacopan treatment resulted in proteinuria reduction and stabilisation of estimated glomerular filtration rate (eGFR) in patients with C3 glomerulopathy. These effects persisted 9 months later, when assessed as part of the extension study. The improvements in kidney function were associated with substantial inhibition of the alternative pathway, thus confirming the mechanism of action of iptacopan.

Added value of this study

Selectively targeting the alternative pathway is considered the optimal approach for modifying the disease course and improving outcomes in patients with C3 glomerulopathy. To the best of our knowledge, APPEAR-C3G is the first randomised phase 3 clinical trial in C3 glomerulopathy, conducted to evaluate the efficacy, safety, and tolerability of iptacopan compared with placebo in addition to supportive care, with or without background immunosuppression in patients with native C3 glomerulopathy. The study aimed to reinforce the positive results from the phase 2 study and the longer-term roll-over extension study.

Implications of all the available evidence

The study results show that iptacopan targets the underlying cause of C3 glomerulopathy by correcting the overactivation of the alternative pathway, decreasing C3 deposition in the kidneys, and demonstrating a clinically meaningful reduction in proteinuria and eGFR stabilisation. Iptacopan showed a rapid onset of action, and the efficacy was sustained to 12 months. Based on real-world evidence, the level of proteinuria reduction and eGFR stabilisation observed with iptacopan in APPEAR-C3G would be expected to decrease the risk of kidney failure in the long term. Based on these efficacy results and acceptable safety profile, iptacopan has the potential to fulfil the unmet need for a targeted treatment for C3 glomerulopathy.

heterogeneous clinical presentation, requiring kidney biopsy to establish diagnosis, and the overall prognosis is poor, with approximately 50% of patients progressing to kidney failure within 10 years of diagnosis.^{2,3}

C3 glomerulopathy is caused by overactivation of the alternative complement pathway in both plasma and the glomerular microenvironment.^{2–5} Such overactivation leads to the accumulation of complement proteins, mainly C3 activation products, in the glomeruli, which triggers kidney inflammation, resulting in glomerular injury.^{2–6} Complement factor B is an essential component of C3 convertase, which drives overactivation of the alternative pathway, and therefore represents a prime target for alternative pathway inhibition.^{6–8}

Before the approval of iptacopan (FABHALTA) for C3 glomerulopathy by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2025,^{9,10} there were no treatment options for C3 glomerulopathy that target the underlying disease pathogenesis. Current guideline recommendations for C3 glomerulopathy rely on supportive treatments—eg, blockade of the renin–angiotensin–aldosterone system (RAAS) with angiotensin-converting enzyme inhibitors or

AT1-receptor blockers, with or without mycophenolic mofetil or corticosteroids.^{3,11} However, evidence related to these supportive treatments is limited to small, retrospective observational studies and such treatments often come with considerable side-effects. Therefore, a concerted effort is required to develop a novel, targeted therapy for C3 glomerulopathy, to address the high unmet medical need for patients with this condition.

Iptacopan (LNP023) is an oral complement inhibitor that targets complement factor B and selectively inhibits the alternative pathway by blocking C3 convertase activity, thus preventing downstream generation of alternative pathway C5 convertase, C3a and C5a anaphylatoxins, and the membrane attack complex.^{12–15} In a phase 2 multicentre study that enrolled 27 patients, 12-week iptacopan treatment resulted in proteinuria reduction and stabilisation of estimated glomerular filtration rate (eGFR) in patients with C3 glomerulopathy.¹⁶ These effects persisted 9 months later, when assessed as part of the extension study.¹⁷

These improvements in kidney function were associated with substantial inhibition of the alternative pathway, thus confirming the mechanism of action of iptacopan.¹⁷ In this study, we aimed to evaluate the efficacy, safety, and tolerability of iptacopan compared with placebo in

addition to supportive care in patients with native C3 glomerulopathy. Along with the published phase 2 results,^{16,17} the phase 3 results described in this Article provided the evidence for approval of iptacopan by the US FDA (in March 2025) and the EMA (in April 2025).

Methods

Study design

APPEAR-C3G was a randomised, double-blind, parallel group, multicentre, placebo-controlled, phase 3 study of iptacopan versus placebo, in addition to supportive care, in adult patients with C3 glomerulopathy. Due to the ultra-rare prevalence of C3 glomerulopathy, the study was conducted in 35 hospitals or medical centres across 18 countries (appendix p 3). Sites were chosen based on their previous clinical trial experience but, given C3 glomerulopathy is an ultra-rare disease, it was expected that most sites would have few cases therefore selection was not based on an expected number of participants and there were no restrictions related to insurance networks. Further details of the study design have been described elsewhere (appendix p 23).¹⁸ The trial was conducted in accordance with the Good Clinical Practice Guidelines of the International Council for Harmonisation and the Principles of the Declaration of Helsinki¹⁹ and ethics approvals were carried out by local Institutional Review Boards or ethics committees (appendix p 32). This trial is registered with ClinicalTrials.gov, NCT04817618. The study protocol is available in the appendix (pp 32–151).

Participants

Adult participants (aged between 18 years and 60 years) with biopsy-confirmed C3 glomerulopathy within 12 months of enrolment as assessed by the investigator and local histopathologist were enrolled into the study. Inclusion criteria included reduced serum C3 concentration (ie, <77 mg/dL [defined as $<0.85 \times$ lower limit of the central laboratory normal range]) at screening, urine protein–creatinine ratio (UPCR) of 1.0 g/g or higher (first morning void urine sample) at day –75 and day –15 before randomisation (which occurred on study day 1), and eGFR of 30 mL/min per 1.73 m² or higher at screening and day –15 before randomisation. Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* before study entry or during the screening period was mandatory. Exclusion criteria included receipt of any cell or solid organ transplantation, rapidly progressive crescentic glomerulonephritis, kidney biopsy showing interstitial fibrosis or tubular atrophy, and monoclonal gammopathy of undetermined significance. The full list of eligibility criteria is available in the appendix (p 6) and further details on the study population are available elsewhere.¹⁸ Before randomisation, all participants received maximally tolerated doses of angiotensin-converting enzyme inhibitors or AT1-receptor blockers for at least 90 days, and vaccinations against encapsulated bacteria. Medications including mycophenolic acids, low-dose

(ie, ≤ 7.5 mg) corticosteroids, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and mineralocorticoid receptor antagonists were allowed when stable for at least 90 days before randomisation. Demographic data on race (White, Black or African American, Asian, Chinese, Indian, Japanese, Korean, Vietnamese, Native Hawaiian or other Pacific Islander, American Indian, or Alaska Native), ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, or unknown), and biological sex at birth (male or female) were self-reported. All participants provided written informed consent.

Randomisation and masking

Participants were enrolled by study investigators. At the randomisation visit, all eligible participants

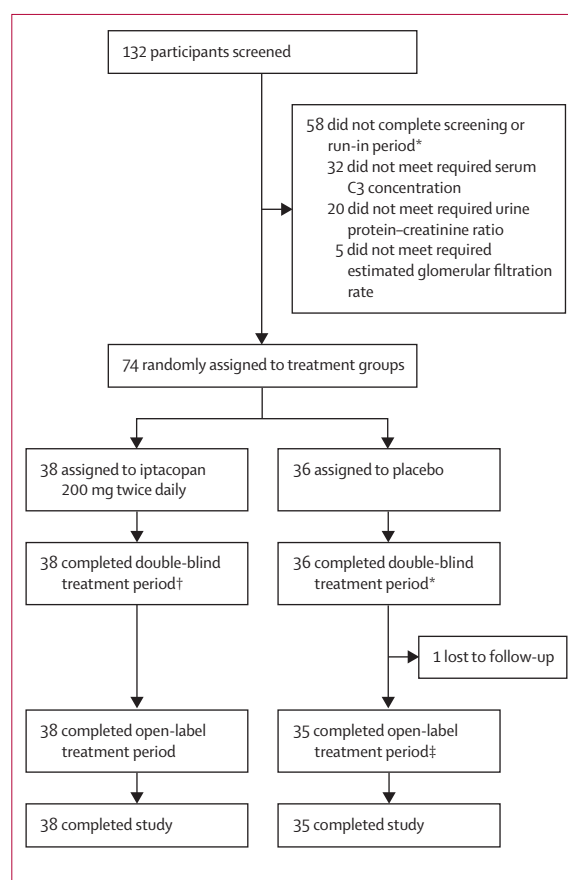


Figure 1: Trial profile

Data are presented for the full analysis set (ie, all participants to whom study treatment was assigned by randomisation). *Some participants did not complete screening or run-in period for more than one reason, the full list includes: did not meet blood pressure criteria; had active hepatitis or abnormal liver function tests; unable to communicate with investigator or comply with study requirements; did not have diagnosis confirmed on renal biopsy within 12 months; was not on stable dose of antiproteinuric medications for 90 or more days; and participant decision. †Two participants randomly allocated to receive iptacopan discontinued treatment in the double-blind period but completed the open-label treatment and the study. ‡One participant randomly allocated to receive placebo discontinued treatment in the open-label period and was lost to follow-up.

	Iptacopan 200 mg (n=38)	Placebo (n=36)
Age (years), mean (SD)	26·1 (10·39)	29·8 (10·79)
Sex		
Male	27 (71%)	20 (56%)
Female	11 (29%)	16 (44%)
Race		
White	27 (71%)	24 (67%)
Black or African American	1 (3%)	1 (3%)
Asian	9 (24%)	9 (25%)
American Indian or Alaska Native	0	1 (3%)
Multiple	0	1 (3%)
Unknown	1 (3%)	0
Region		
North America	7 (18%)	8 (22%)
Europe	22 (58%)	19 (53%)
Other	9 (24%)	9 (25%)
Ethnicity		
Hispanic or Latino	1 (3%)	6 (17%)
Not Hispanic or Latino	34 (89%)	29 (81%)
Not reported	2 (5%)	0
Unknown	1 (3%)	1 (3%)
Baseline 24-h UPCR (g/g), geometric mean (95% CI)	3·33 (2·79–3·97)	2·58 (2·18–3·05)
Baseline 24-h UPCR (3 g/g)		
<339 g/mol	17 (45%)	25 (69%)
≥339 g/mol	21 (55%)	11 (31%)
Baseline 24-h total urinary protein (3 g/day)		
<3000 mg/day	11 (29%)	15 (42%)
≥3000 mg/day	27 (71%)	21 (58%)
Baseline eGFR (mL/min per 1·73 m ²), mean (SD)	89·3 (35·20)	99·2 (26·88)
Baseline eGFR		
<60 mL/min per 1·73 m ²	10 (26%)	4 (11%)
≥60 mL/min per 1·73 m ²	28 (74%)	32 (89%)

(Table 1 continues in next column)

were randomised via interactive response technology to one of the two treatment groups. The interactive response technology assigned a randomisation number to the participant, which was used to link the participant to a treatment group and specified a unique medication number for the first package of study treatment dispensed to the participant as well as unique medication kit numbers for all study treatments dispensed at later visits. Randomisation was stratified by treatment with corticosteroids, mycophenolic acid, or both (yes or no) to ensure that the proportion of participants being treated with these agents was similar in the iptacopan and placebo treatment groups. Participants, investigator staff, individuals performing the assessments, and the clinical trial team were masked to treatment assignment from the time of randomisation until the interim database lock, after all

	Iptacopan 200 mg (n=38)	Placebo (n=36)
(Continued from previous column)		
Baseline eGFR		
<90 mL/min per 1·73 m ²	19 (50%)	12 (33%)
≥90 mL/min per 1·73 m ²	19 (50%)	24 (67%)
Has hypertension	23 (61%)	18 (50%)
Sitting systolic blood pressure (mm Hg), mean (SD)	125·8 (13·30)	122·6 (11·43)
Sitting diastolic blood pressure (mmHg), mean (SD)	77·7 (8·77)	77·7 (8·47)
Baseline C3 (mg/L), mean (SD)	316·8 (243·41)	339·3 (227·96)
Age at C3 glomerulopathy diagnosis (years), mean (SD)	22·0 (10·88)	25·3 (10·80)
Years since C3 glomerulopathy diagnosis		
<2 years	15 (39%)	15 (42%)
≥2 years	23 (61%)	21 (58%)
C3 glomerulopathy subtype at diagnosis		
C3 glomerulonephritis	26 (68%)	32 (89%)
Dense deposit disease	9 (24%)	1 (3%)
Mixed C3 glomerulonephritis and dense deposit disease	2 (5%)	2 (6%)
Unknown	1 (3%)	1 (3%)
Corticosteroid treatment, mycophenolic acid treatment, or both, at time of random allocation	16 (42%)	17 (47%)

Data are n (%) unless otherwise indicated. Baseline 24-h UPCR refers to UPCR as measured by the geometric mean of two 24-h urine collections at baseline. Baseline 24-h total urinary protein refers to total urinary protein as measured by the geometric mean of two 24-h urine collections at baseline. Baseline eGFR was defined as the arithmetic mean of two eGFR values at the day -15 visit (before randomisation) and the day 1 visit. Hypertension is defined based on hypertension at diagnosis, as reported by the investigator on the C3 glomerulopathy medical history case report form and the pre-defined hypertension terms taken from patient medical history. eGFR=estimated glomerular filtration rate. UPCR=urine protein-creatinine ratio.

Table 1: Baseline characteristics

participants had completed the double-blind treatment period. Sponsor staff were also masked to treatment assignment. Unblinding could occur in case of participant emergencies and at the conclusion of the double-blind treatment period.

Procedures

In the iptacopan group, participants took 200 mg iptacopan orally (formulated as a 200 mg capsule) twice daily (morning and evening) for 6 months (double-blind) followed by open-label iptacopan at 200 mg twice daily for an additional 6 months. In the placebo group, participants took placebo orally (formulated as a 200 mg matching capsule) twice daily for 6 months (double-blind) followed by open-label iptacopan 200 mg twice daily orally for an additional 6 months (appendix p 23). Iptacopan and matching placebo capsules were supplied by Novartis Pharma Produktions (Wehr, Germany) to investigator sites as double-blind study drug

kits. Scheduled study visits occurred at days 14, 30, 90, and 180 during the double-blind period and days 210, 270, and 360 during the open-label period. Assessments included UPCR, eGFR, alternative pathway biomarkers, and clinical laboratory variables (the full assessment schedule is available in the appendix p 14–15). The study also required mandatory renal biopsies during the screening period (day 45) and at 6 months to evaluate changes in total activity score and C3 deposit score. Additional information on the study methodology is available in the appendix (pp 7–8).

Outcomes

For the double-blind period, the primary endpoint was relative reduction in proteinuria (as measured by log-transformed ratio to baseline in UPCR sampled from a 24-h urine collection) between groups at 6 months. Secondary outcomes for the double-blind period were difference in eGFR (change from baseline at 6 months) and proportion of participants who achieved a composite renal endpoint (stable or improved eGFR [$\leq 15\%$ reduction] compared with the baseline visit and $\geq 50\%$ reduction in UPCR from baseline to 6 months). Additional secondary objectives were effect of iptacopan versus placebo in reducing glomerular inflammation in the kidney (change from baseline in disease total activity score in a renal biopsy at 6 months) and on patient-reported fatigue (change from baseline to 6 months in the FACIT-Fatigue score), and to evaluate the safety profile and tolerability of iptacopan compared with placebo during the 6-month double-blind period. An adverse event was defined as any untoward medical occurrence (eg, any unfavourable and unintended sign, symptom, or disease). The investigators were tasked with providing the severity of the adverse event (mild, moderate, or severe), causality as it related to study treatment, duration, whether it met criteria for a serious adverse event (ie, required or prolonged hospitalisation), action taken with study treatment, and the outcome of the adverse event. The occurrence of adverse events was sought by non-directive questioning of the participant at each visit during the study by investigators or their designees. Adverse events were also detected when they were volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments. The adverse event terms provided by the investigators were classified further based on MedDRA dictionary version 27.0.

Exploratory outcomes for the double-blind period were to evaluate the change in serum C3 with iptacopan compared with placebo (log-transformed ratio to baseline in serum C3 at 6 months), evaluate the effect of iptacopan compared with placebo on glomerular C3 deposition (change from baseline in glomerular C3 deposit and total chronicity scores from a renal biopsy at 6 months), and the effect of iptacopan versus placebo on plasma and urinary complement biomarkers (change from

baseline in log-transformed plasma and urinary sC5b-9 at 6 months).

For the open-label period, the primary outcome was to evaluate the effect of iptacopan on proteinuria at 12 months (change from baseline in log-transformed UPCR at the 12-month visit [both study treatment groups] and from the 6-month to the 12-month visit in the placebo group). The secondary outcomes were to evaluate the effect at 12 months of iptacopan on the composite renal endpoint and the safety profile and tolerability of iptacopan during the 6-month open-label treatment period as well as the entire 12-month treatment period. Exploratory outcomes for the open-label period were to assess the longer-term effects of iptacopan on change in eGFR, change in eGFR slope before and after iptacopan initiation in the overall study population, and change in complement biomarkers. Except for eGFR values collected before screening that were included in the exploratory eGFR

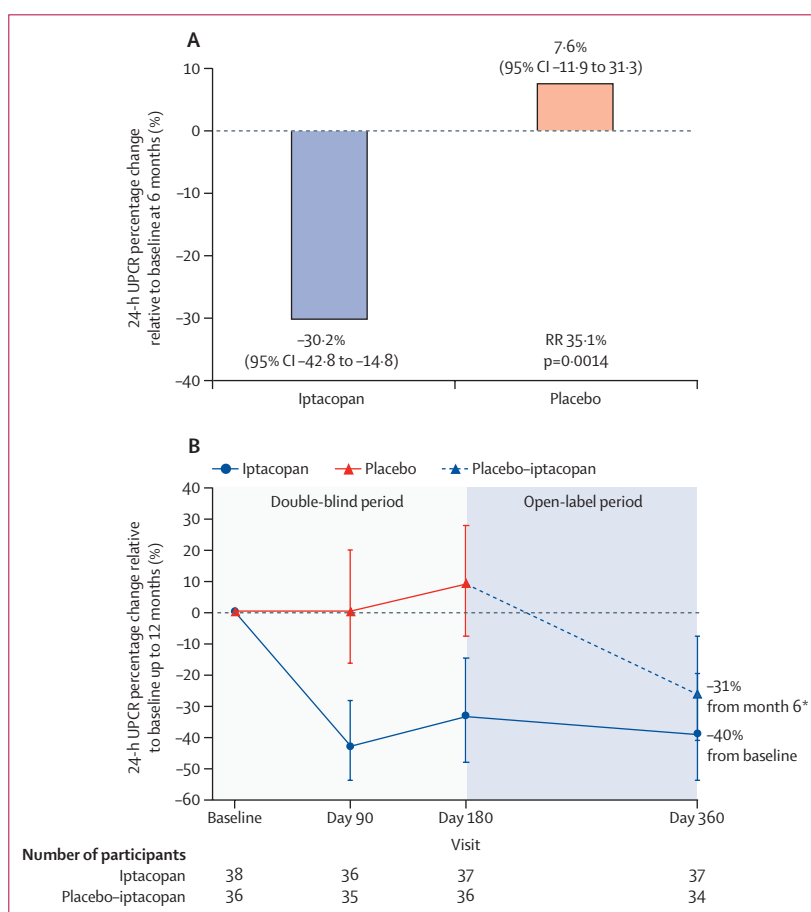


Figure 2: Percentage change in proteinuria (24-h UPCR) following treatment of iptacopan or placebo relative to baseline at 6 months (A) and up to 12 months (B)

Data are presented for the full analysis set (ie, all participants to whom study treatment was assigned by randomisation). (A) The model estimated geometric mean of the ratio to baseline in percentage change (95% CI) of UPCR 24 h (g/g) at month 6 by treatment group (full analysis set). (B) Plot of percentage change (95% CI) of 24 h UPCR (g/g), up to month 12 by treatment group (full analysis set). RR=relative reduction. UPCR=urine protein-creatinine ratio. *Based on the analysis using the combined full analysis set (ie, all participants to whom study treatment was assigned by randomisation).

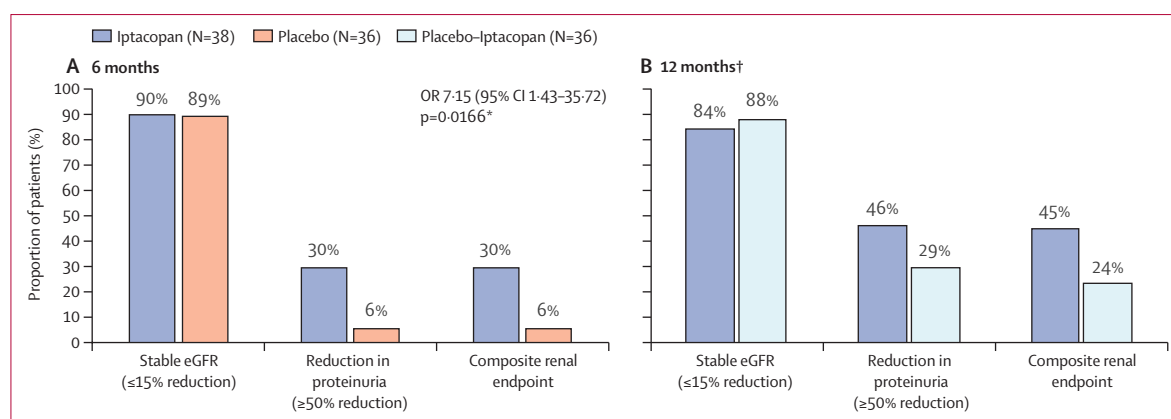


Figure 3: The proportion of patients that achieved the composite renal endpoint (ie, $\geq 50\%$ reduction UPCR and $\leq 15\%$ reduction in eGFR) at 6 months (A) and 12 months (B)

Data are presented for the full analysis set (ie, all participants to whom study treatment was assigned by randomisation). eGFR=estimated glomerular filtration rate. OR=odds ratio. UPCR=urine protein-creatinine ratio. *Statistically significant after adjustment for multiple testing. †12 months of treatment in those randomised initially to iptacopan and 6 months iptacopan treatment in those randomised initially to placebo.

slope analyses, all UPCR, eGFR, and biomarkers were assessed at a central laboratories. The lists of study outcomes and endpoints for the double-blind and open-label periods are available in the appendix (pp 16–17).

Statistical analysis

The sample size calculation was performed to ensure adequate statistical power to test the primary outcome (superiority of iptacopan versus placebo on proteinuria reduction), as previously described,¹⁸ and detailed in the appendix (p 9). The primary analysis was performed for the log ratio to baseline in 24-h UPCR (iptacopan vs placebo) using a Mixed Model for Repeated Measures model and tested at one-sided 0.025 significance level. A multiple test procedure was used for testing the hypotheses associated with four secondary endpoints: change from baseline in eGFR, proportion achieving composite renal endpoint, change in disease total activity score, and change in FACIT-Fatigue score at 6 months. The hypotheses associated with the secondary endpoints were to be tested only if the null hypothesis associated with the primary endpoint was rejected. Analyses of the primary and secondary efficacy endpoints have been described previously.¹⁸ The primary analyses were performed on the full analysis set (ie, all participants to whom study treatment was assigned by randomisation); all participants who received at least one dose of study treatment were included in the safety analysis. All analyses were carried out as per the study protocol or as prespecified in the statistical analysis plan (appendix pp 152–259). Details on the statistical hypotheses, models, and analysis methods are available in the appendix (pp 8–11, 23). All statistical analyses were performed with SAS (version 9.4). An independent data monitoring committee was established and routinely reviewed unblinded safety data at 4-month intervals.

Role of the funding source

The funder designed the trial with input from the steering committee that included some of the academic authors (DK, ASB, MV, and RJHS). The investigators gathered the data, which were analysed by the funder. All authors and the funder contributed to each draft of the manuscript, with medical writing assistance funded by the sponsor. The sponsor provided iptacopan and matched placebo.

Results

Between July 28, 2021, and Feb 15, 2023, 132 participants were screened, of whom 58 (44%) did not complete the screening and run-in period and 74 (56%) were randomised 1:1 to receive either iptacopan (n=38) or placebo (n=36; figure 1). Two participants randomised to the iptacopan group discontinued treatment in the double-blind period but resumed treatment in the open-label period, going on to complete the open-label treatment and the study. One participant in the placebo group discontinued treatment during the open-label period as per participant decision and was lost to follow-up. All 74 participants randomly assigned to treatment groups completed the 6-month double-blind period (appendix p 18); 73 participants completed the 12-month study (double-blind and open-label period).

Participant baseline characteristics and demographics are presented in table 1. Of the 74 participants, 47 (64%) were male, 51 (69%) were of White race, 41 (55%) were from the European region, and 63 (85%) were not of Hispanic or Latino ethnicity. The mean age of all participants was 27.9 years (SD 10.68). Baseline proteinuria was higher and eGFR was lower in the iptacopan group (table 1). Systolic and diastolic blood pressures were well controlled (table 1; appendix pp 18, 24). In the 2 years preceding randomisation, 73 (99%) of 74 participants in the overall study population

were taking RAAS inhibitors for a median of 413 days (range 18–730; appendix p 19). 33 (45%) participants were taking immunosuppressants (ie, mycophenolic mofetil or mycophenolic acid) for a median of 497 days (93–730) or corticosteroids for a median of 246 days (51–730), or both (appendix p 19).

The primary outcome of the study was met, demonstrating superiority of iptacopan over placebo in proteinuria reduction at 6 months. In the iptacopan group, 24-h UPCR was 3.33 g/g (95% CI 2.79 to 3.97) at baseline and 2.17 g/g (1.62 to 2.91) at 6 months; in the placebo group, 24-h UPCR was 2.58 g/g (2.18 to 3.05) at baseline and 2.80 g/g (2.37 to 3.30) at 6 months. The relative reduction in 24-h UPCR was 35.1% (95% CI 13.8 to 51.1; $p=0.0014$) following 6 months of treatment with iptacopan compared with placebo (figure 2A). The 24-h UPCR percentage change relative to baseline at 6 months was -30.2% (95% CI -42.8 to -14.8) in the iptacopan group and 7.6% (-11.9 to 31.3) in the placebo group. One participant randomly assigned to iptacopan required an increase in background immunosuppression (increase in corticosteroid dose) during the double-blind period, and proteinuria data collected after the increase in corticosteroid dose were imputed in the primary analysis. 27 (73%) of 37 participants in the iptacopan group showed absolute reduction in proteinuria (24-h UPCR) from baseline at month 6 (appendix p 25).

A beneficial treatment effect of iptacopan on 24-h UPCR at 6 months was observed in several key participant subgroups (appendix p 26). Results from the supplementary analysis of the UPCR first morning void data were consistent with the primary analysis based on 24-h UPCR at 6 months. Due to more frequent sampling, a rapid onset of proteinuria reduction (first morning void data) could be observed at the first post-randomisation assessment (day 14; appendix p 27).

The proportion of participants who reached the composite endpoint at 6 months was 11 (30%) of 37 participants in the iptacopan group versus two (6%) of 32 participants in the placebo group, resulting in a 7.15-fold (95% CI 1.43–35.72) increase in the odds of achieving the composite renal endpoint compared with placebo ($p=0.0166$). These results were primarily driven by the 24-h UPCR component, with most participants in both treatment groups having stable eGFR at 6 months (figure 3A).

At baseline mean eGFR was 89.3 mL/min per 1.73 m² in the iptacopan group and 99.2 mL/min per 1.73 m² in the placebo group. The change in eGFR at 6 months was 1.30 mL/min per 1.73 m² in the iptacopan group compared with -0.86 mL/min per 1.73 m² in the placebo group. There was a difference of 2.16 mL/min per 1.73 m² (95% CI -2.75 to 7.06; $p=0.3241$) in eGFR at 6 months for iptacopan versus placebo (figure 4A). The change in eGFR at 6 months adjusted for baseline UPCR was evaluated in a post-hoc analysis (appendix p 28).

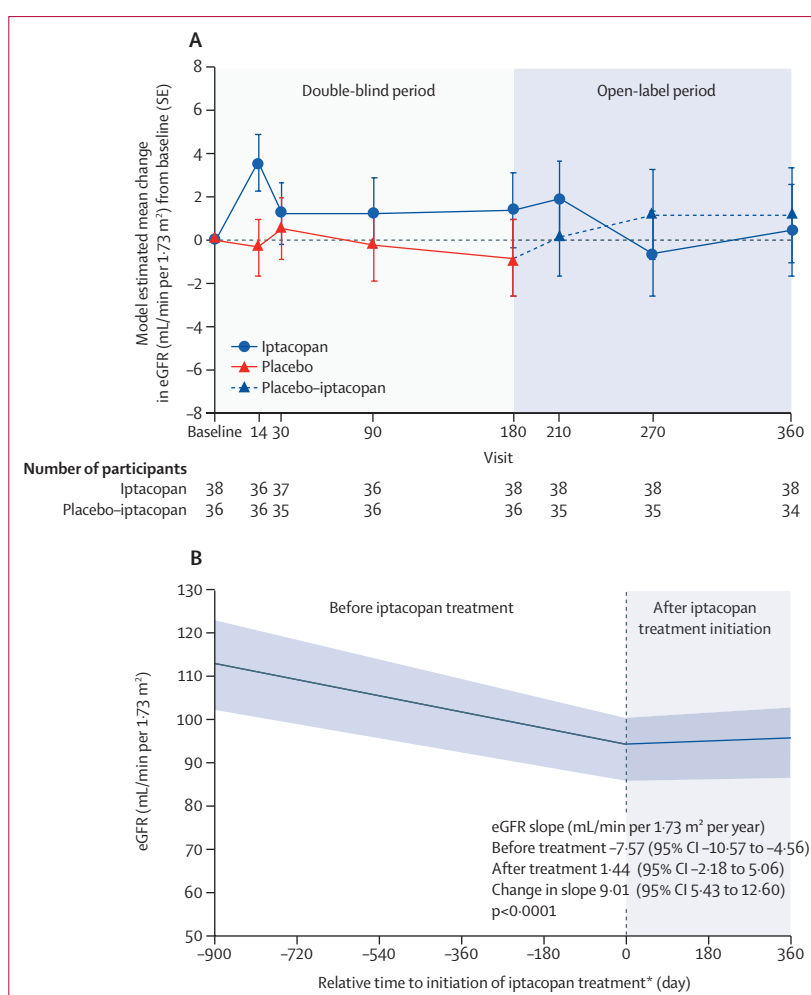


Figure 4: Effect of iptacopan 200 mg twice daily versus placebo on eGFR (N=74)

(A) Model estimated mean change from baseline (\pm SE) of eGFR (mL/min per 1.73 m²) by treatment up to month 12. (B) Annualised eGFR slope change for all patients. Data are presented for the full analysis set (ie, all participants to whom study treatment was assigned by randomisation). The thick line represents the mean value and the shaded area represents the 95% CI. Historical data were collected up to 2 years before the start of randomisation. eGFR=estimated glomerular filtration rate. *Treatment initiation occurred on day 0.

FACIT-Fatigue scores at baseline were in the normal range in the iptacopan group, mean score 42.4 (SD 10.08), and the placebo group, mean score 41.9 (8.91), and remained stable at 6 months, with no statistically significant ($p=0.9310$) change observed for iptacopan versus placebo (appendix p 13).

The mean change in C3 glomerulopathy histological index total activity score after 6 months of treatment with iptacopan was -1.95 versus -1.11 in the placebo group (adjusted mean difference -0.83 [95% CI -1.87 to 0.21]; $p=0.2895$; appendix p 29). The decline in total activity score was principally driven by reductions in endocapillary proliferation and leukocyte infiltration in the capillaries and mesangium in favour of iptacopan (appendix pp 13, 20).

Prespecified, exploratory analysis showed that baseline C3 immunofluorescence intensity was

elevated in both the iptacopan group (mean intensity 9.2 [SD 2.9; on a scale of 0–12]) and the placebo group (mean intensity 9.6 [SD 2.9]). The adjusted mean change from baseline to 6 months in C3 deposit score was -0.78 (95% CI -1.81 to 0.25) in the iptacopan group and 1.09 (0.11 to 2.08) in the placebo group. Iptacopan reduced glomerular C3 deposition, as shown by an adjusted mean difference for iptacopan versus placebo of -1.88

(-3.30 to -0.45) in the C3 deposit score at 6 months ($p=0.0053$).

In other prespecified exploratory analyses, iptacopan significantly increased serum C3 (185.2% [95% CI 125.7 – 260.2]), decreased plasma sC5b-9 (66.3% [56.5 – 73.8]), and decreased urinary sC5b9:creatinine (81.6% [62.4 – 91.0]) at 6 months compared with placebo ($p\leq 0.0001$ for all three biomarkers). Similarly to the trend observed with proteinuria first morning void reduction (appendix pp 12, 27), there was rapid effect of iptacopan treatment observed at the first post-randomisation assessment at day 14 (figure 5C).

For the open-label period, participants in the iptacopan group had a baseline to 12 month sustained reduction of 40% in 24-h UPCR, showing durability of the treatment effect observed at 6 months (figure 2B). This proteinuria reduction from baseline at 12 months (37%) was confirmed using Mixed Model for Repeated Measures analysis (appendix p 12). The reduction of 24-h UPCR in participants originally randomly assigned to placebo (the placebo–iptacopan group) was 31% between day 180 and day 360 (after receiving 6 months of iptacopan in the open-label period). These reductions in proteinuria were in addition to maximally tolerated doses of RAAS inhibitors and use of immunosuppression in approximately half the study population with minimal changes in these medications during the treatment period (appendix p 21).

Similar to the double-blind period, reduction in proteinuria from the supplementary analysis of the UPCR first morning void data was consistent with the primary analysis based on 24-h UPCR at 12 months (appendix p 12, 27).

Between 6 months and 12 months, the proportion of participants who met the composite renal endpoint increased from 30% (11/37) to 45% (17/38) in the iptacopan group and from 6% (2/32) to 24% (8/34) in the placebo–iptacopan group (figure 3B).

Compared with baseline, 12-month data indicated that eGFR remained stable in the iptacopan group. The adjusted mean changes from baseline in eGFR in the iptacopan group was 0.44 mL/min per 1.73 m² (95% CI -3.76 to 4.64) and 1.15 mL/min per 1.73 m² (-3.22 to 5.53) in the placebo–iptacopan group at 12 months (figure 4A).

Historical serum creatinine data over the 2 years before study randomisation were systematically collected for all 74 participants and were used to calculate eGFR using the CKD-EPI formula (appendix p 7), consistent with the calculation of eGFR during the study. These data allowed a robust comparison of the annualised eGFR slope before the initiation of iptacopan treatment and the slope after the start of treatment. In the prespecified analysis (appendix pp 11, 199, 221), the mean pretreatment annualised eGFR slope showed rapid decline with -7.57 mL/min per 1.73 m²/year (95% CI -10.57 to -4.56 ; figure 4B).

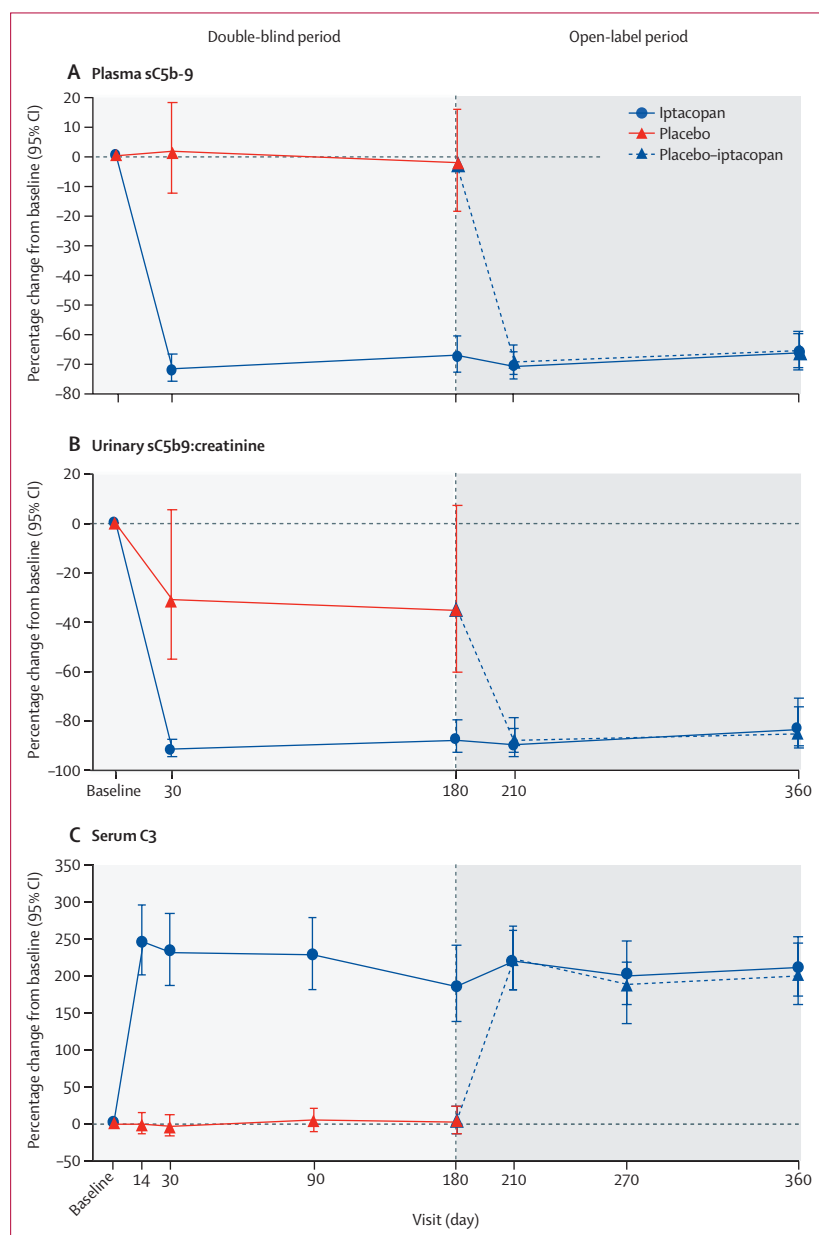


Figure 5: Effect of iptacopan 200 mg twice daily versus placebo on concentrations of plasma sC5b-9 (A), urine sC5b-9:creatinine (B), and serum C3 (C) up to month 12 by treatment group

Data are presented for the full analysis set (ie, all participants to whom study treatment was assigned by randomisation). Percentage change is supplied as the model estimated geometric mean of the ratio to baseline in percentage change of each complement biomarker at designated timepoints by treatment group.

	Iptacopan 200 mg (n=38)	Placebo (n=36)
Number of participants with at least one treatment-emergent adverse event	30 (79%)	24 (67%)
Mild	19 (50%)	21 (58%)
Moderate	9 (24%)	2 (6%)
Severe	2 (5%)	1 (3%)
Suspected to be related to study medication	7 (18%)	4 (11%)
Serious adverse events	3 (8%)	1 (3%)
Blood culture positive for <i>Streptococcus pneumoniae</i>	1 (3%)	0
Infected bite	1 (3%)	0
Chest discomfort	1 (3%)	0
Acute kidney injury	0	1 (3%)
Ascites	0	1 (3%)
Adverse events leading to study drug discontinuation	0	0
Deaths	0	0

Data are n (%). All participants with non-missing baseline and covariates were included in the safety analysis. A patient with multiple occurrences for an adverse event is only counted once. Adverse events for the 12-month period are provided in the appendix (p 22).

Table 2: Adverse events during the 6-month double-blind treatment period

Following commencement of iptacopan treatment (12 months of treatment in participants randomised initially to iptacopan and 6 months in those randomised initially to placebo), there was stabilisation of annualised eGFR slope at 1.44 mL/min per 1.73 m²/year (−2.18 to 5.06), equating to a predicted preservation of eGFR of 9.01 mL/min per 1.73 m²/year (5.43 to 12.60) compared with the scenario where iptacopan had not been commenced and eGFR continued to deteriorate at the pretreatment rate. A post-hoc analysis of the change in eGFR slope by individual treatment groups at 6 months is described in the appendix (pp 12, 30).

In prespecified exploratory analyses at 12 months in the iptacopan group, there was a sustained increase from baseline in serum C3 by 211% (95% CI 172–254), and a sustained reduction from baseline in both urinary sC5b-9:creatinine by 84% (71–91) and plasma sC5b-9 by 66% (60–72). The effect was replicated in the placebo group after initiation of iptacopan treatment (figure 5; appendix p 13).

Iptacopan was well tolerated during the 6-month double-blind period (table 2). There were no deaths reported, no discontinuations due to treatment-emergent adverse events, and no meningococcal infections. 30 (79%) of 38 participants in the iptacopan group had treatment-emergent adverse events, as did 24 (67%) of 36 participants in the placebo group. Most participants had treatment-emergent adverse events of mild (19 [50%] in the iptacopan group; 21 [58%] in the placebo

group) or moderate (nine [24%] in the iptacopan group; two (6%) in the placebo group) severity. Overall, three (8%) participants in the iptacopan group and one (3%) participant in the placebo group had serious adverse events in the double-blind period. There were two reported infection-related serious adverse events, both in the iptacopan group (table 2).

For the open-label period; the overall frequency of adverse events in the combined safety set was similar to that reported in the 6-month double-blind treatment period (appendix p 22). One participant, who tested blood culture positive for *S pneumoniae* in the double-blind period, had a pneumococcal infection in the open-label period, which were both resolved with a standard course of antibiotics (appendix pp 13, 22). Infection with encapsulated organisms is an important risk associated with all complement inhibitors, including iptacopan.

Discussion

Current treatment guidelines for C3 glomerulopathy as established by expert opinion and based on observational data from a small number of patients show limited effectiveness and highlight the substantial unmet need for novel therapies.^{3,11} At the time of writing, iptacopan has been approved for the treatment of adults with paroxysmal nocturnal haemoglobinuria, the treatment of adults with C3 glomerulopathy, and for the reduction of proteinuria in adults with primary IgA nephropathy.⁹ Iptacopan became the first approved treatment for C3 glomerulopathy with approvals from both the FDA and EMA in early 2025,^{9,10} whereas pegcetacoplan (targeting C3) received approval from the FDA in July, 2025.²⁰ Based on its mechanism of action, oral iptacopan targets the underlying cause of C3 glomerulopathy pathophysiology. The results of this phase 3 study in C3 glomerulopathy show benefit on both proteinuria reduction and eGFR.

Proteinuria has been identified in numerous studies to be a marker of kidney damage and a risk factor for progression to kidney failure in many glomerular diseases.^{21–23} In the past 5 years, similar analyses have concluded that reductions in proteinuria slow disease progression and lower the risk of kidney failure in C3 glomerulopathy.^{24–27} For example, the Spanish GLOSEN registry data showed that a reduction in UPCr at 6 months or 12 months predicted a reduction in the rate of kidney failure.²⁸ Attainment of the composite renal endpoint in our study was largely driven by the proteinuria response to iptacopan. The observed magnitude of proteinuria reduction has been linked to favourable short-term and long-term outcomes in C3 glomerulopathy.^{24–27} Furthermore, a rapid reduction of proteinuria (first morning void data) was observed following iptacopan treatment.

In ultra-rare kidney diseases, it is not feasible to power studies to evaluate the benefit on delaying kidney failure, but fortunately eGFR slope has been shown to predict

longer term risk of kidney failure.²⁹ In the past 5 years, studies in C3 glomerulopathy have also shown that an eGFR slope between -2 mL/min per 1.73 m² per year and -10 mL/min per 1.73 m² per year is associated with an increased risk of kidney failure compared with an eGFR slope of 0 .²⁷ In the current study, the pretreatment eGFR slope based on historical data showed a rapid slope decline, which stabilised after treatment with iptacopan. The pretreatment slope is consistent with the natural history of C3 glomerulopathy: up to 50% of patients progress to kidney failure over 10 years.^{2,3} Furthermore, the pretreatment slope in the APPEAR-C3G population is consistent with real-world data on the rate of decline in eGFR in the GLOSEN and RaDaR studies.^{24–27} In addition, the data from RaDaR and GLOSEN suggest that the stabilisation of eGFR slope achieved with iptacopan would be expected to decrease the risk of kidney failure in C3 glomerulopathy.^{24–27}

Mechanistically, iptacopan showed a fast and sustained downregulation of the alternative pathway, evidenced by the complement alternative pathway biomarker data. Coupled with a reduction in C3 deposits, these data support iptacopan as a targeted treatment at the root cause of the disease.

Iptacopan was well tolerated and had an acceptable safety profile. There were no deaths, no treatment discontinuations due to treatment-emergent adverse events, and even though a higher proportion of participants had treatment-emergent adverse events in the iptacopan group, most treatment-emergent adverse events were mild to moderate in severity. Infections caused by encapsulated bacteria are an increased risk during complement inhibition.³⁰ The two serious treatment-related pneumococcal infections in a single participant in the study resolved with a standard course of antibiotics. There were no cases of meningitis or meningococcal sepsis. The safety profile of iptacopan in the APPEAR-C3G trial is consistent with that observed across other studies in C3 glomerulopathy and studies in other diseases (IgA nephropathy and paroxysmal nocturnal haemoglobinuria).^{16,17,31–33}

A key strength of APPEAR-C3G is that it is a randomised, placebo-controlled trial in an ultra-rare disease. In addition, the study population represented a high-risk population of patients with heavy proteinuria despite standard of care treatment at study entry. There are important limitations to the study findings. The mean change in eGFR did not achieve statistical significance, probably due to the preserved eGFR in the study population at baseline and the short double-blind period (see appendix p 7 for further details on the rationale for study design). The change in eGFR from pretreatment to post-treatment provides an alternative method of evaluating the benefit of iptacopan, although the pretreatment eGFR values are based on historical creatinine values collected before study enrolment. The eGFR slope analysis by treatment group showed that the iptacopan group had stabilisation of the

slope during the double-blind period, whereas the placebo group continued to show eGFR decline albeit less severe than the pretreatment period, which could be a result of more frequent monitoring and better adherence to supportive treatment including RAAS inhibitors, and background immunosuppression within the structured trial environment. The double-blind period of 6 months also limits the ability to demonstrate meaningful outcome data on some histopathology endpoints. For example, some components of total activity score, such as endocapillary proliferation and leukocyte infiltration, are likely to change within 6 months, whereas other components take longer, and there was no change in fibrosis, tubular fibrosis, or crescents as these had low baseline scores based on exclusion criteria. As the FACIT-Fatigue score at baseline was comparable to the normal population, this limited the ability to find a difference in fatigue between the two treatment groups and no statistical differences were observed after 6 or 12 months of iptacopan treatment. In addition, the study entry criteria required low serum C3 at study entry even though patients with C3 glomerulopathy might present with normal serum C3 concentrations.³⁴ However, based on its mechanism of action, iptacopan is expected to be efficacious regardless of serum C3 concentration as patients with normal C3 concentrations have the same disease pathology with overactivation of the alternative pathway at tissue level.³⁴ Lastly, in the study population, 69% of patients were White and 55% were from the European region, which limits the generalisability of the results.

The phase 3 trial of iptacopan versus placebo, both in addition to standard of care treatments, showed a statistically significant and clinically meaningful proteinuria reduction at 6 months, along with stabilisation of eGFR and reduction in C3 deposits. Iptacopan was also shown to have a fast and sustained effect on downregulating the alternative pathway and was well tolerated with a favourable safety profile. The positive results presented here provide evidence that iptacopan targets the underlying cause of C3 glomerulopathy and has the potential to alter the course of this progressive disease and improve patient outcomes.

Contributors

All authors had access to the study data. DK, CMN, RKI, YW, IK, and IS have accessed and verified the patient-level study data. DK, ASB, MV, CMN, GR, M-HZ, EKSW, YW, IK, AJT, NJAW, MM, and RJHS were involved in the conceptualisation of the published work. YW, IK, and IS participated in data curation. YW and IK conducted the formal analysis. DK, ASB, MV, CMN, GR, M-HZ, EKSW, IS, and RJHS participated in research and investigation process. DK, ASB, MV, and RJHS contributed to the methodology. IS was involved in project administration. YW was responsible for software programming, testing, and implementation. All authors participated in the validation and visualisation of the published work. All authors were involved in writing, reviewing, and editing the original and subsequent drafts of the published work. All authors were responsible for the final decision to submit the manuscript for publication.

Declaration of interests

DK is scientific founder of and holds stock in Gyroscope Therapeutics; received consultancy income from Achillion, Alexion, AstraZeneca, Catalyst, Chemocentryx, Novartis, Roche, and Silence Therapeutics;

received grants or contracts from Gyroscope Therapeutics, Kidney Research UK, Macular Society, Medical Research Council, and Wellcome Trust; and his spouse works for GSK. ASB has received consulting honoraria from Achillion, Alexion, Amgen, Apellis, Catalyst, GSK, Novartis, Otsuka, and Silence Therapeutics. MV has received honoraria for advisory boards and consulting fees and participated as Principal Investigator in clinical studies sponsored by the following pharmaceutical companies: Achillion, Alexion, Apellis, Bayer, Biocryst Pharmaceuticals, Chemocentryx, Chinook Therapeutics, GSK, Novartis, PureSpring, Retrophin-Traverse, Roche, Santhera, Sobi, and Vifor. CMN has received clinical trial research support from Achillion, Apellis, Biocryst Pharmaceuticals, Novartis, and Traverse; received consulting fees from Alexion, Apellis, Novartis, Silence Therapeutics, and Vertex; and participated on the data safety monitoring board of Kira. GR has received consulting fees from Alexion, BioCryst Pharmaceuticals, and Sobi. M-HZ has received honoraria for consulting boards and consulting fees from AstraZeneca, BeiGene, Kira, Novartis, Roche, and SanReno Therapeutics. EKSJW has received fees for consultancy or speakers' agreements from Alexion, Apellis, Arrowhead, Biocryst Pharmaceuticals, Sobi, and Novartis. RJHS has received research funding from National Institutes of Health and is a consultant for Novartis. MM, YW, NJAW, AJT, IK, IS, and RKI were employees and stockholders of Novartis at time of manuscript preparation. NJAW and MM were employees of Novartis at the time of study completion.

Data sharing

Novartis provides access to the complete de-identified patient data set accompanied by a data dictionary following requests submitted via <https://clinicalstudydatarequest.com/Default.aspx>. Data are available for request after European Medicines Agency and US Food and Drug Administration (FDA) drug approval, or 18 months after trial completion, whichever is latest. Additional supporting documents, such as the clinical study protocol (with any amendments), the annotated case report form, the reporting and analysis plan, dataset specifications, and the clinical study report will also be made available following requests submitted via <https://clinicalstudydatarequest.com/Default.aspx>, after European Medicines Agency and US FDA drug approval or 18 months after trial completion, whichever is later.

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