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Iptacopan in Idiopathic Immune Complex–Mediated Membranoproliferative Glomerulonephritis: Protocol of the APPARENT Multicenter, Randomized Phase 3 Study

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Introduction: Immune complex–mediated membranoproliferative glomerulonephritis (IC-MPGN) is an ultra-rare, fast-progressing kidney disease that may be idiopathic (primary) or secondary to chronic infection, autoimmune disorders, or monoclonal gammopathies. Dysregulation of the alternative complement pathway is implicated in the pathophysiology of IC-MPGN; and currently, there are no approved targeted treatments. Iptacopan is an oral, highly potent proximal complement inhibitor that specifically binds to factor B and inhibits the alternative pathway (AP).

Methods: This randomized, double-blind, placebo-controlled phase 3 study (APPARENT; NCT05755386) will evaluate the efficacy and safety of iptacopan in patients with idiopathic (primary) IC-MPGN, enrolling up to 68 patients (minimum of 10 adolescents) aged 12 to 60 years with biopsy-confirmed IC-MPGN, proteinuria $\geq$1 g/g, and estimated glomerular filtration rate (eGFR) $\geq$30 ml/min per 1.73 m^2. All patients will receive maximally tolerated angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and vaccination against encapsulated bacteria. Patients with any organ transplant, progressive crescentic glomerulonephritis, or kidney biopsy with >50% interstitial fibrosis/tubular atrophy, will be excluded. Patients will be randomized 1:1 to receive either iptacopan 200 mg twice daily (bid) or placebo for 6 months, followed by open-label treatment with iptacopan 200 mg bid for all patients for 6 months. The primary objective of the study is to evaluate the efficacy of iptacopan versus placebo in proteinuria reduction measured as urine protein-to-creatinine ratio (UPCR) (24-h urine) at 6 months. Key secondary end points will assess kidney function measured by eGFR, patients who achieve a proteinuria-eGFR composite end point, and patient-reported fatigue.

Conclusion: This study will provide evidence toward the efficacy and safety of iptacopan in idiopathic (primary) IC-MPGN.

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Membranoproliferative glomerulonephritis is a rare histologic pattern of glomerular injury characterized on kidney biopsy by the findings of hypercellularity, endocapillary proliferation, and endocapillary wall thickening with double contour formation with light microscopy.[1,2] There has been subsequent classification of membranoproliferative glomerulonephritis into IC-MPGN, resulting from immunoglobulin/immune complex deposition triggering complement activation, and complement 3 (C3) glomerulopathy (C3G), resulting from dysregulation in the AP of the complement system leading to isolated or

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predominant C3 deposition with little or no immunoglobulin deposition.[1,2] At present, the mechanism by which the immune complexes are formed in these diseases is unknown. In its primary idiopathic forms, IC-MPGN shares with C3G overlapping pathophysiological features, with dysregulation of the AP strongly implicated in the pathogenesis of both conditions[2-6]; both also have similar clinical presentations and outcomes.[2,7]

Because IC-MPGN may be secondary (i.e., caused by immunoglobulin deposition in the mesangium and along the capillary walls as a result of autoimmune disease, chronic infection, or a monoclonal gammopathy/paraprotein-related disease),[2,8] in the work-up of this glomerular disease, careful investigation of secondary causes is essential because treatment should be directed at the underlying causal condition.[9] When a clear etiology cannot be identified, IC-MPGN is classified as idiopathic (primary), and a genetic and serological work-up for complement AP dysregulation is warranted as well as ideally, a targeted therapy addressing the underlying pathophysiology.[9]

The onset of IC-MPGN is typically seen in children and young adults,[10,11] although it can occur at any age.[12,13] Affected individuals have a reported 9% to 41% risk of kidney failure within 10 years and face a substantial risk of recurrence after kidney transplantation (43% recurrence).[7,14] A recent study from the Spanish Nephrology Society's Glomerular Diseases Study Group, reporting outcomes in patients with IC-MPGN and C3G receiving a kidney transplant, showed that 37% reached kidney failure at a median follow up of 79 months.[15] Disease recurrence was a key driver of failure and occurred in 62% of patients with C3G and 15% of patients with idiopathic (primary) IC-MPGN.[15] In patients with C3G, a faster rate of decline in eGFR is associated with higher probability of kidney failure.[16]

Despite the high risk of kidney failure with IC-MPGN and C3G,[17] there are currently no approved therapies that target the underlying cause of these conditions. The complement system plays a key role in immunosurveillance and tissue homeostasis[18] and can be activated by 3 distinct pathways: classical pathway, activated by immune complexes; lectin pathway, triggered by microbial polysaccharides; and AP,[19] which is constitutively active, making it particularly susceptible to complement dysregulation.[20] Importantly, the AP also plays a pivotal role in amplifying the complement response and may account for >80% of terminal pathway activation regardless of the activating pathway.[21]

Dysregulation of the AP is implicated in both idiopathic (primary) IC-MPGN and C3G. Activation of the AP is believed to play a role in the pathophysiology of idiopathic (primary) IC-MPGN in addition to that of the classical complement pathway, which is triggered by the immune-complex deposition.[3] In IC-MPGN, glomerular deposition of immune complexes owing to persistent antigenemia triggers classical pathway complement activation and C3 deposition.[13] Dysregulation of the AP is typically sustained by genetic abnormalities, which are observed in 10% to 25% of patients with IC-MPGN,[5,7,10,13] or acquired disease drivers (nephritic factors), which comprise a heterogenous group of antibodies against C3 or C5 convertases with the capacity to stabilize the molecule, prolong its half-life and thus cause dysregulation of the AP of complement.[3,5,10,13,14] These findings suggest that targeting AP activation by inhibiting or preventing the formation of C3 convertase may be a potential therapeutic strategy for idiopathic (primary) forms of IC-MPGN.

Iptacopan (LNP023) is an oral, first-in-class, highly potent proximal complement inhibitor that specifically binds to factor B and efficiently blocks the AP (Figure 1).[22-24] Inhibition of complement factor B prevents activity of AP-related C3 convertase and the subsequent formation of C5 convertase.[18,22] Although iptacopan does not block activation of the classical pathway or lectin pathway, it does inhibit their recruitment of the AP amplification loop.[22,25] In clinical trials, iptacopan has been found to be well-tolerated in first-in-human studies.[26,27] In a phase 2 study, iptacopan treatment for 12 weeks resulted in a mean increase in eGFR of 3.1 ml/min per 1.73 m^2 from baseline in patients with native C3G, corresponding to a mean predicted eGFR preservation of 6.4 ml/min per 1.73 m^2, together with a significant 45% reduction in proteinuria and a significant reduction in the histologic C3 deposit score in follow-up kidney biopsy in patients with recurrent C3G post-transplant at week 12.[28] Of the 26 patients who entered the extension study, in those with native C3G, long-term treatment (12 months) with iptacopan resulted in further proteinuria reduction (57% [$P < 0.0001$]) and eGFR improvement (by +6.83 ml/min per 1.73 m^2 [$P = 0.0174$]) beyond that previously reported following 12 weeks of treatment, whereas in patients with recurrent post-transplant C3G, eGFR remained stable with long-term iptacopan.[29] These results support the rationale for further evaluating the benefits of iptacopan in IC-MPGN.

Here, we describe the rationale and design of a phase 3 trial that aims to evaluate the clinical efficacy and safety of iptacopan compared with placebo in adolescent and adult patients with IC-MPGN.

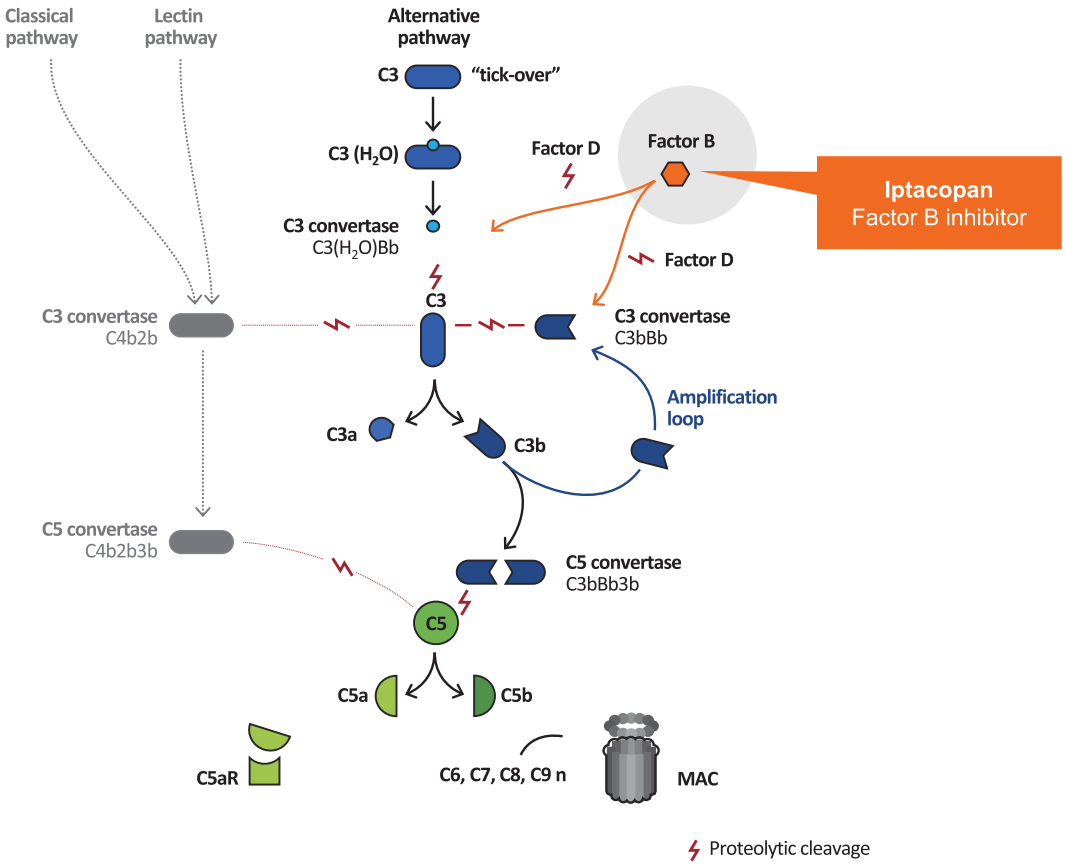

Figure 1. Targeting complement in IC-MPGN.[24] Iptacopan, a factor B inhibitor, specifically binds to factor B and efficiently blocks the alternative pathway. FB, factor B; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis; MAC, membrane attack complex.

METHODS

Study Population

Up to 68 participants (including adults and minimum of 10 adolescents) will be randomized 1:1 to either the iptacopan or placebo treatment arm. All patients are to provide written consent and fulfill all the criteria for inclusion and meet no exclusion criteria (Table 1). For all adult and adolescent participants in the study, the diagnosis of IC-MPGN must be based on a kidney biopsy within 12 months before enrollment in adults, and within 3 years of enrollment in adolescents (a biopsy report, review, and confirmation by the Investigator is required). The requirement for a renal biopsy within 12 months is due to the potential for changes in the histopathological features of IC-MPGN over time. Biopsy helps to confirm the diagnosis and ensure that the participant has a clear diagnosis of membranoproliferative glomerulonephritis with histological features that meet study eligibility criteria. If an adult's original biopsy is >12 months old, a repeat biopsy must be obtained at screening. However, for adolescents, a biopsy within 3 years is allowed because it may not be ethical or practical to repeat a biopsy in this population. The use of cyclosporine, tacrolimus, rituximab, other calcineurin inhibitors, and other standard immunosuppressive therapy (except mycophenolic acids [mycophenolate mofetil or mycophenolate sodium]) is prohibited during the entire study. However, their prior use is allowed, as long as they are discontinued before screening, at least 90 days before randomization. The use of mycophenolic acids is prohibited during the study in India. If the participant must be treated with any of these agents during the course of the study, the study drug must be discontinued before and during the administration of the agent. The study protocol permits the use of sodium/glucose cotransporter-2 inhibitors, mycophenolic acids (except in India) and oral prednisolone <7.5 mg daily at any time during the course of the study. However, the dose of these agents should be stable for at least 90 days before randomization and throughout the study drug treatment period. Female participants who are pregnant or breastfeeding or intending to conceive during the study will be excluded from the study because of the lack of safety data.

Study Design

This multicenter, randomized, double-blind, parallel-group, placebo-controlled, pivotal phase 3 study (APPARENT; NCT05755386) will evaluate the efficacy and safety of iptacopan in patients with idiopathic (primary) IC-MPGN (Figure 2). This study will be

Table 1. Key inclusion and exclusion criteria

Inclusion	Exclusion
Age ≥12 and ≤60 years at screening	Any solid organ or cell transplantation, including kidney transplantation
Biopsy-confirmed diagnosis of idiopathic (primary) IC-MPGN in the past 12 months for adults and in the past 3 years for adolescents	Patients diagnosed with secondary IC-MPGN, including but not limited to any of the following conditions: deposition of antigen-antibody immune complexes as a result of chronic viral, bacterial, and protozoa/other infections; autoimmune diseases (such as systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, and mixed connective tissue disease); monoclonal gammopathy; and fibrillary glomerulonephritis
On maximally recommended dose of ACEI or ARB for at least 90 days	Rapidly progressive crescentic glomerulonephritis (50% decline in the eGFR within 3 months) with renal biopsy findings of glomerular crescent formation seen in ≥50% of glomeruli
UPCR ≥1.0 g/g (≥113 mg/mmol)	Acute postinfectious glomerulonephritis
eGFR[a] or measured GFR ≥30 ml/min per 1.73 m^2	Renal biopsy showing interstitial fibrosis/tubular atrophy >50%
Vaccination against *Neisseria meningitidis, Streptococcus pneumoniae,* and *Haemophilus influenzae* infections	Use of complement inhibitors (e.g., factor B, factor D, C3 inhibitors, anti-C5 antibodies, and C5a receptor antagonists) within 6 months before the screening visit Use of immunosuppressants (except mycophenolic acids), cyclophosphamide or systemic prednisone at a dose >7.5 mg/day (or equivalent) within 90 days of study drug administration
	Monoclonal gammopathy of undetermined significance
	Adults: SBP <80 mm Hg or >160 mm Hg, or DBP <50 mm Hg or >100 mm Hg, or pulse rate <45 bpm or >100 bpm Adolescents: SBP <80 mm Hg or >150 mm Hg, or DBP <50 mm Hg or >95 mm Hg, or pulse rate <50 bpm or >110 bpm
	Body mass index >38 kg/m^2; body weight <35 kg
	Liver disease, infection liver injury History of recurrent invasive infections caused by encapsulated organisms Human immunodeficiency virus infection Evidence of urinary obstruction or difficulty in voiding Severe concurrent comorbidities or medical condition deemed likely to interfere with study participation

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis; SBP, systolic blood pressure; UPCR, urine protein-to-creatinine ratio.
[a]Using the Chronic Kidney Disease Epidemiology Collaboration formula for patients aged ≥18 years and modified Schwartz formula for patients aged 12–17 years.

conducted in approximately 80 sites in 18 countries across North America, South America, Europe, and Asia, according to International Council for Harmonization E6 Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki.

An independent data monitoring committee will regularly assess the progress of the study, the safety data, and recommend whether to continue, modify, or terminate the trial.

The study comprises 3 periods: a screening/run-in period of up to 90 days; a 360-day treatment period (comprising 6 months of randomized double-blinded treatment and then 6 months of open-label treatment); and a 30-day safety follow-up (or optionally, transition to the extension study NCT03955445). The study treatment phase comprises a 6-month blinded period (either iptacopan 200 mg [dosing for adolescents will be 2 × 100 mg capsules] bid or placebo) followed by a 6-month open-label period (iptacopan 200 mg bid) (Figure 2). Patients will be randomized 1:1 to one of the treatment arms and will receive either iptacopan 200 mg bid or matching placebo. Participants, investigators, staff, and the clinical trial team (performing assessments) and sponsors remain blinded from the time of randomization until database lock after all participants have completed the double-blind treatment period. Randomization will be stratified by corticosteroid or mycophenolic acid treatment at randomization. As per the study protocol, further stratification by other variables is not considered necessary because multiple stratification parameters would result in imbalances in small strata or overstratification.

The identity of the treatment will be concealed by the use of study treatments that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

Assessments

All adolescent participants will undergo blood pressure and heart rate monitoring on day 1 with the first dose of blinded study drug (iptacopan 200 mg or placebo) and on day 180. These cardiovascular parameters will be recorded for 1 hour before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours after dosing. If persistent increases in heart rate or changes in blood pressure occur, the study drug will be discontinued for the participant. Randomization will be stratified by corticosteroid and/or mycophenolic acid treatment at randomization in the adult cohort.

A summary of key study assessments is provided in Table 2.

Kidney function will be assessed by proteinuria as measured by UPCR from a 24-hour urine collection, UPCR-eGFR composite renal end point, and eGFR. Urine will be collected over a 24-hour period on days 1

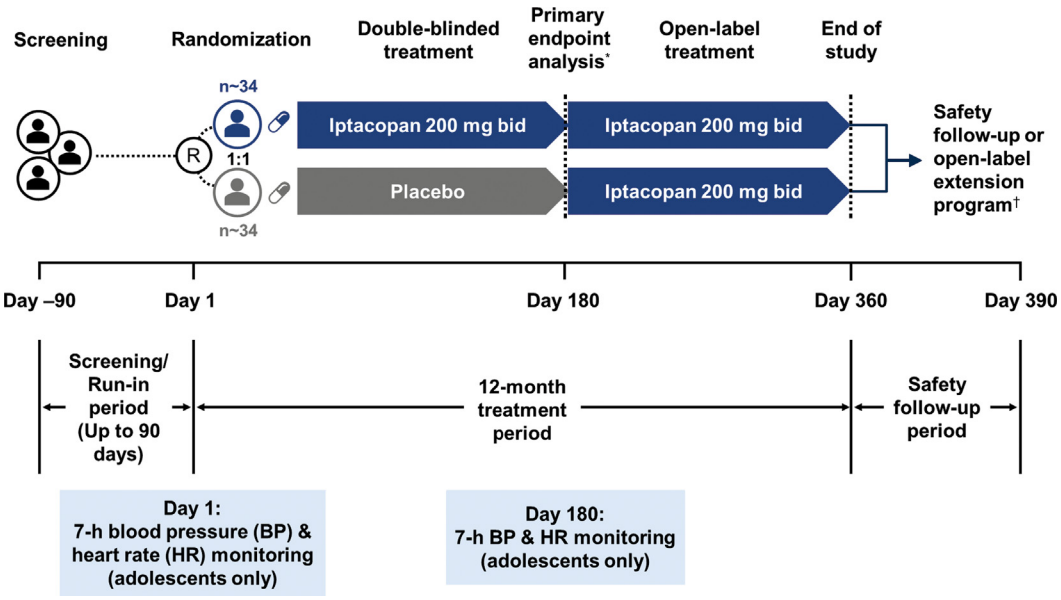

Figure 2. Study design. *The primary analysis for the study will be performed when all randomized participants have completed the 6-month double-blind treatment period. A final analysis will be conducted after all participants have completed the 6-month open-label period (i.e., after either 6 months or 1 year on iptacopan).
†A 30-day safety follow-up period or transition to an open-label extension study (CLNP023B12001B; NCT03955445).

(baseline), 90, 180, and 360. Duplicate 24-hour urine tests will be performed at baseline and at 6 months to minimize risks associated with collection error for the primary end point. The effect of iptacopan on serum C3 and other complement pathway biomarkers (Bb and sC5b-9) will also be assessed as exploratory outcomes.

The primary patient-reported outcome for this study is the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue). The purpose of FACIT-Fatigue in this study is to assess the experience and effect of fatigue on patients with IC-MPGN. To further understand the participants' symptoms, functioning, and overall well-being, as well as their changes during the study, Short-Form 36 and EuroQol-5 dimensions-5 levels questionnaires will be completed. To further support the determination of minimum important change for the FACIT-Fatigue, 1 additional single question of Patient Global Impression of Severity will be included. In addition, a patient interview will be conducted within 7 days after the 6-month visit to validate these patient-reported outcomes. This interview allows patients to give feedback on their experience of meaningful changes in their condition and patient-reported outcome measures, and it is optional.

Table 2. Summary of study assessments

Assessment category	Assessment
Efficacy	Proteinuria (UPCR) eGFR Composite renal end point (1) a stable or improved eGFR compared with baseline visit (≤15% reduction in eGFR); and (2) a ≥50% reduction in UPCR compared with baseline visit] Patient-reported outcome – (FACIT-Fatigue) score
Key safety	Adverse event monitoring Laboratory evaluations (blood and urine) Electrocardiogram Cardiovascular surveillance (adolescents only)
Other	Complement pathway and renal injury biomarkers Patient-reported outcomes – SF-36, EQ-5D-5L and PGIS Iptacopan levels at trough (PK assessment)

eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol-5 dimensions-5 levels; FACIT-Fatigue, functional assessment of chronic illness therapy-fatigue; PGIS, patient global impression of severity; PK, pharmacokinetic; SF-36, Short-Form 36; UPCR, urine protein–creatinine ratio.

Study Objectives

The primary objective of the double-blind period is to demonstrate the superiority of iptacopan versus placebo in reducing proteinuria at 6 months with the primary end point being the log-transformed ratio to baseline in UPCR (sampled from a 24-h urine collection) at 6 months (Table 3). The primary objective of the open-label period is to assess the effect of iptacopan on proteinuria at 12 months (Table 3). Primary end points for the open-label period are the log-transformed ratio to baseline in UPCR at the 12-month visit (both study treatment arms) and the log-transformed ratio to 6-month visit in UPCR, at the 12-month visit in the placebo arm (iptacopan treatment period).The secondary objective for both double-blind and open-label period is to demonstrate the superiority of iptacopan versus placebo in improving eGFR, the proportion of patients achieving a composite renal end point (a stable or improved eGFR [≤15% reduction in eGFR] and a ≥50% reduction in UPCR compared with the baseline visit), patient-reported fatigue, to perform cardiovascular surveillance (adolescents only), and to

Table 3. Objectives and related end points for the double-blind and open-label treatment periods

	Objectives	End points
Double-blind period		
Primary objective	To demonstrate the superiority of iptacopan vs. placebo on reducing proteinuria at 6 months	Log-transformed ratio to baseline in UPCR (sampled from a 24-h urine collection) at 6 months
Secondary objectives	To demonstrate the superiority of iptacopan vs. placebo on improvement from baseline in eGFR at 6 months	Change from baseline in eGFR at 6 months
	To demonstrate the superiority of iptacopan vs. placebo in the proportion of patients who achieve a composite renal end point at 6 months	A participant meets the requirements of the composite renal end point if they satisfy the following criteria at the 6-month timepoint: (i) a stable or improved eGFR compared with baseline visit (≤15% reduction in eGFR) and (ii) a ≥50% reduction in UPCR compared with baseline visit
	To assess the effect of iptacopan vs. placebo on patient reported fatigue at 6 months	Change from baseline to 6 months in the FACIT-Fatigue score
	To assess the effect of iptacopan versus placebo on BP, HR, cardiac function, and biomarkers of cardiac injury in adolescents	Changes in HR, mean sitting DBP and msSBP, ECG parameters, and N-terminal pro-brain natriuretic peptide
	To evaluate the safety and tolerability of iptacopan vs. placebo during the 6-month double-blind period	Vital signs, ECGs, laboratory measurements, AEs, AESIs, and AE-related study drug discontinuation
Open-label period		
Primary objective	To evaluate the effect of iptacopan on proteinuria at 12 months	Log-transformed ratio to baseline in UPCR at the 12-month visit (both study treatment arms) Log-transformed ratio to 6-month visit in UPCR at the 12-month visit in the placebo arm (iptacopan treatment period)
Secondary objectives	To evaluate the effect of iptacopan at 12 months on: • Improvement from baseline in eGFR • The proportion of patients who achieved a composite renal end point • Improvement of patient-reported fatigue	Change from baseline in eGFR at 12 months (both arms) and change in eGFR from 6 months to 12 months in the placebo arm (iptacopan treatment period) Proportion of patients who meet the criteria of achieving the composite renal end point at 12 months in both arms and from 6 months to 12 months in the placebo arm (iptacopan treatment period) Change from baseline in the FACIT-Fatigue score at 12 months in both arms and from 6 months to 12 months in the placebo arm (iptacopan treatment period)
	To assess the effect of iptacopan versus placebo on BP, HR, cardiac function, and biomarkers of cardiac injury in adolescents during the open-label period	Changes in HR, mean sitting DBP and msSBP, ECG parameters, and N-terminal pro-brain natriuretic peptide
	To evaluate the safety and tolerability of iptacopan during the open-label period as well as the whole treatment period	Vital signs, ECGs, laboratory measurements, AEs, AESIs, and AE-related study drug discontinuation

AEs, adverse events; AESIs, adverse events of special interest; BP, blood pressure; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FACIT-Fatigue, functional assessment of chronic illness therapy-fatigue; HR, heart rate; msSBP, mean sitting systolic blood pressure; UPCR, urine protein–creatinine ratio.

evaluate the safety and tolerability of iptacopan. The key secondary objectives and end points for the double-blind and open-label periods are also shown in Table 3.

Statistical Considerations

The primary analysis will be performed when all randomized participants have completed the 6-month double-blind treatment period. This analysis will determine the efficacy of iptacopan compared with placebo in decreasing proteinuria, stabilizing eGFR, and inhibiting the overactive AP. The primary end point will be analyzed using the full analysis set according to the randomized treatment group as assigned at randomization. The mean difference between iptacopan and placebo will be estimated from a mixed model for repeated measures. A supplementary analysis for the primary end point will use a 'Bayesian dynamic borrowing' approach, which incorporates a robust mixture prior to distribution and allows for dynamic borrowing of prior information from the C3G phase 3 study (NCT04817618). [24] The analysis will learn how much of the C3G prior information to borrow based on the consistency of the IC-MPGN and the C3G data.

A final analysis will be conducted after all participants have completed the 6-month open-label period (i.e., after either 6 months or 1 year on iptacopan). This analysis will provide insights on the persistence of efficacy and an assessment of the safety profile of iptacopan over a longer period of treatment.

Sample Size

We calculated the sample size to ensure enough power for testing superiority of iptacopan versus placebo in proteinuria reduction (the primary end point of log-transformed ratio to baseline in UPCR at 6 months). Assuming a reduction in UPCR at 6 months of 50% in the iptacopan group versus 20% in the placebo group (i.e., a relative reduction vs. placebo in UPCR of 37.5%) and an SD of 0.69 (on the log-scale), a sample size of 34 participants per group (total 68 participants) provides at least 80% power at a 1-sided significance level of 0.025. Therefore, the study will enroll approximately 68 adult and adolescent patients aged 12 to 60 years

with biopsy-confirmed idiopathic (primary) IC-MPGN. The study population will consist of a minimum of 10 adolescents (12–17 years old) enrolled in the countries and sites as per local requirements.

DISCUSSION

This pivotal phase 3 study will provide evidence toward the efficacy and safety of iptacopan in idiopathic (primary) IC-MPGN. There have been relatively few clinical trials so far that have evaluated the potential benefits of selective anticomplement therapies in IC-MPGN (including C3G or other similar diseases) and progressed beyond phase 1.[30-33] This dearth reflects the rare nature of this disease, the incomplete understanding of the natural clinical course as well as the learning process within the clinical community on relevant end points. Advances in the design of clinical trials will answer many of the current questions and aid regulatory agencies in defining the path for registration of novel therapies for the treatment of idiopathic (primary) IC-MPGN.

All complement inhibiting drugs are known to increase risk of infection by encapsulated bacteria; thus, the requirement for vaccination when using these agents. However, as iptacopan inhibits factor B activity and prevents AP-related C3 convertase and the subsequent formation of C5 convertase,[18,22] this results in blocking the amplification of the classical and lectin complement pathways while leaving direct signaling intact[22] and, thus, the infection risk is theoretically lower. Interim analysis of an open-label phase 2 study in patients with treatment-naïve paroxysmal nocturnal hemoglobinuria found that iptacopan monotherapy resulted in normalization of hemolytic markers and rapid transfusion-free improvement of hemoglobin levels in most patients; and no serious or severe adverse events, including none of an infectious nature, were reported.[34] Confirmatory phase 3 trials in paroxysmal nocturnal hemoglobinuria (APPLY-PNH; NCT04558918[23]; APPOINT-PNH; NCT04820530[35]) are completed.

The key efficacy assessments being used in this study of urinary protein excretion and eGFR are widely used measures of kidney function and indicators of disease progression. Proteinuria is a marker for kidney damage and a risk factor for progression to kidney failure in other glomerular diseases;[36,37] and the level of proteinuria is considered a reliable predictor of treatment effect on long-term outcome in other chronic kidney diseases such as diabetic kidney disease, immunoglobulin A nephropathy, focal segmental glomerulosclerosis, and idiopathic membranous nephropathy. Furthermore, a recent analysis in patients with C3G showed that doubling proteinuria levels was associated with a 2.5-fold increase in the risk of kidney failure, whereas reduction of at least a 50% in proteinuria lowered this risk of disease progression.[38] The same group has reported that in patients with C3G, a faster rate of decline in eGFR is associated with a higher probability of kidney failure.[16]

The assessment of change from baseline in eGFR at 6 months in this trial is a key secondary end point in this trial and is supported as a surrogate end point by the National Kidney Foundation in other glomerular diseases and is being investigated by the Kidney Health Initiative.[39,40] Therefore, the evaluation of the primary end point of log-transformed ratio to baseline in UPCR (sampled from a 24-h urine collection) at 6 months is considered to be sufficient to detect meaningful differences between participants treated with iptacopan compared with placebo. In a phase 2 study, iptacopan treatment for 12 weeks resulted in a reduction in proteinuria and an increase in eGFR from baseline in patients with native C3G;[28] and of the 26 patients who entered the extension study, 12-month treatment with iptacopan resulted in further reduction in proteinuria and improvement in eGFR in those with native C3G, while eGFR remained stable in patients with recurrent post-transplant C3G.[29]

Almost all patients who have progressive kidney disease have diminished quality of life; therefore, from a patient's perspective, improved quality of life is a priority. As a result of this, the study design contains the patient-centric quality of life outcome measures of FACIT-Fatigue, EQ-5D5L total and Short-Form 36 questionnaires, and Patient Global Impression of Severity score to provide insight into efficacy from a patient perspective. One of the most commonly reported symptoms among patients with chronic kidney disease and renal insufficiency progressing toward kidney failure is fatigue,[41] which has also been shown to improve in parallel with reduction of proteinuria.[42,43] Therefore, the inclusion of the FACvIT-Fatigue Scale to assess the experience and effect of fatigue on patients with IC-MPGN. During the study, a range of complement pathway biomarkers and autoantibodies, including C4d, sC5B9, Fragment Bb, C3, C4, Wieslab, and AutoAB (C3Nefs, Anti Fb, and anti C3) will be measured. These data will be used to explore any potential correlations between the presence or absence of genetic abnormalities/autoantibodies and treatment response to iptacopan in idiopathic (primary) IC-MPGN. This analysis will be exploratory in nature, and the data will be used accordingly. The identification of any such correlations could help in the development of personalized treatment plans for patients with this rare disease entity. In addition, these data may provide insights into the role of genetic abnormalities and autoantibodies in the pathogenesis of idiopathic (primary) IC-MPGN beyond complement inhibition.

As of today, there is no established standard-of-care for patients with IC-MPGN because of the rare nature of the disease and the paucity of evidence-based treatment.[9] Therefore, the need for specific therapies that target the underlying cause of this disease to improve patient outcomes. The design of the APPARENT trial, including the use of surrogate end points such as proteinuria and eGFR slope as well as patient-reported outcomes, will provide evidence toward the efficacy and safety of iptacopan in IC-MPGN and will contribute to therapy development in complement-mediated kidney diseases. By selectively inhibiting complement factor B and subsequently preventing overactivation of the AP to slow chronic kidney disease progression, iptacopan has an outstanding potential to be the first targeted therapy to become available to patients with idiopathic (primary) forms of IC-MPGN.

DISCLOSURE

MV declares honoraria for advisory boards and consulting fees. Participation in clinical studies is sponsored by the following pharmaceutical companies: Achillion, Alexion, Apellis, Bayer, Catalyst, Novartis, Roche, Retrophin/Travere, GSK, BioCryst Pharmaceuticals, Chinook Therapeutics, Purespring, and Vifor. ASB declares consulting honoraria from Achillion, Alexion, Chemocentryx, Novartis, Silence, Catalyst, and Principio. RJHS declares research funding from NIH and being a consultant for Novartis. DK is a scientific founder of and holds stocks in Gyroscope Therapeutics; he has received consultancy income from Gyroscope Therapeutics, Alexion Pharmaceuticals, Novartis, Apellis, and Sarepta; and his spouse works for GSK. MM, YW, NW, and UKV are employees and stockholders of Novartis.

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