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Targeting the Alternative Complement Pathway With Iptacopan to Treat IgA Nephropathy: Design and Rationale of the APPLAUSE-IgAN Study

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Introduction: Targeting the alternative complement pathway (AP) is an attractive therapeutic strategy because of its role in immunoglobulin A nephropathy (IgAN) pathophysiology. Iptacopan (LNP023), a proximal complement inhibitor that specifically binds to factor B and inhibits the AP, reduced proteinuria and attenuated AP activation in a Phase 2 study of patients with IgAN, thereby supporting the rationale for its evaluation in a Phase 3 study.

Methods: APPLAUSE-IgAN (NCT04578834) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study enrolling approximately 450 adult patients (aged ≥18 years) with biopsy-confirmed primary IgAN at high risk of progression to kidney failure despite optimal supportive treatment. Eligible patients receiving stable and maximally tolerated doses of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) will be randomized 1:1 to either iptacopan 200 mg or placebo twice daily for a 24-month treatment period. A prespecified interim analysis (IA) will be performed when approximately 250 patients from the main study population complete the 9-month visit. The primary objective is to demonstrate superiority of iptacopan over placebo in reducing 24-hour urine protein-to-creatinine ratio (UPCR) at the IA and demonstrate the superiority of iptacopan over placebo in slowing the rate of estimated glomerular filtration rate (eGFR) decline (total eGFR slope) estimated over 24 months at study completion. The effect of iptacopan on patient-reported outcomes, safety, and tolerability will be evaluated as secondary outcomes.

Conclusions: APPLAUSE-IgAN will evaluate the benefits and safety of iptacopan, a novel targeted therapy for IgAN, in reducing complement-mediated kidney damage and thus slowing or preventing disease progression.

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IgAN is the most prevalent form of primary glomerulonephritis, characterized by dominant or codominant deposition of galactose-deficient IgA in the glomerular mesangium.[1,2] IgAN typically affects young adults and is one of the leading causes of kidney failure, with 15% to 40% of patients developing kidney failure within 10 to 20 years of diagnosis,[3–7] thereby placing considerable socioeconomic burden on individuals, caregivers, and health care systems globally.[8]

Despite the significant burden and frequency of kidney failure associated with IgAN, until recently, there were no approved targeted treatments for IgAN. Supportive care with renin-angiotensin system

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inhibitors to control blood pressure and proteinuria remains the standard of care for managing adult patients with IgAN and proteinuria >0.5 g/d.[9] Systemic corticosteroids may be considered for patients at high risk of disease progression (defined as persistent proteinuria >0.75–1 g/d despite ≥90 days of optimized supportive care) based on individual benefit or harm assessment.[9] Historically, the evidence on the risk or benefit profile of corticosteroids in IgAN has been inconclusive, and their use has been associated with increased risk of treatment-emergent toxicity.[9] The recently published TESTING study results suggest that reducing the dose of corticosteroids (from 0.8 mg/kg/d [maximum 48 mg/d] to 0.4 mg/kg/d [maximum 32 mg/d]) could maintain efficacy while improving tolerability[10]; however, reduced-dose steroids in this study were still associated with substantial toxicity compared with placebo.[10] A delayed-release formulation of budesonide, a corticosteroid, has recently received accelerated approval and conditional approval in the United States and European Union (EU) for reducing proteinuria in adult patients with IgAN who are at risk of rapid disease progression.[11–13] However, a greater incidence of corticosteroid-related adverse events (AEs), albeit milder than those observed with systemic corticosteroids, was observed with budesonide versus placebo in clinical trials,[11–13] highlighting the continued need to identify safer, effective pharmacotherapies in IgAN. With an improved understanding of the disease pathogenesis, several pharmacotherapies with novel mode of action are being evaluated to address this unmet need.[14]

Dysregulation of the complement system plays a pivotal role in the onset and progression of IgAN. Notably, there is strong evidence for the involvement of the AP in most patients and the lectin pathway (LP) in some patients.[15,16] Glomerular co-deposition of complement 3 (C3) and its degradation products, along with IgA-containing immune complexes, is observed in >90% of biopsies of patients diagnosed with IgAN.[15] Key regulators of AP such as properdin, factor H, and factor H-related (FHR)1, and FHR5 are also found in glomerular immune deposits, supporting the role of the AP in the pathogenesis of IgAN.[16] The presence of FHR5 and absence of factor H deposits correlates with disease progression.[16,17] Genetic association studies provide compelling evidence of the role of AP in IgAN that deletions in complement FHR1 and FHR3 genes (*CFHR1*, *CFHR3*) confer protection against IgAN.[17] Conversely, variants of *CFH* that lead to lower plasma factor H levels may predispose IgAN development.[15] These observations demonstrate that targeting AP is an attractive therapeutic strategy to slow or halt disease progression in IgAN.

Iptacopan (LNP023) is a proximal complement inhibitor that specifically binds factor B (FB) and inhibits the AP (Figure 1).[18] FB is a positive regulator of the AP and is the catalytically active component of AP C3 and C5 convertases. Inhibition of FB prevents activity of AP C3 convertase and the subsequent formation of AP C5 convertase. In turn, this prevents downstream cell destruction, inflammation, excessive complement deposition, and consequent kidney damage.[18] While iptacopan inhibits amplification of the classical pathway (CP) and LP, it leaves direct signaling intact.[18] In the recent Phase 2 study of iptacopan in patients with IgAN, iptacopan inhibited AP activation and reduced proteinuria by approximately 23% (80% confidence interval: 8%–34%) versus placebo after 3 months of treatment. Proteinuria continued to decrease with longer treatment duration.[19,20] Similarly, iptacopan treatment for 3 months reduced proteinuria by 45% in patients with C3 glomerulopathy and native kidneys in a Phase 2 study.[21,22] Iptacopan has been well tolerated in clinical studies across multiple indications thus far.[20–23]

Here, we describe the rationale and design of the Phase 3 APPLAUSE-IgAN trial, which aims to evaluate the effect of iptacopan on proteinuria reduction, eGFR decline, and health-related QoL in adults with IgAN.

METHODS

Study Population

This global study will enroll approximately 450 adult patients (≥18 years) with biopsy-confirmed (within up to 5 years) primary IgAN at high risk of progression to kidney failure despite optimal supportive treatment. The main study population consists of approximately 430 patients with an eGFR ≥ 30 ml/min per 1.73 m^2 and UPCR ≥ 1 g/g at baseline and would form the basis of efficacy and safety analyses. In addition, approximately 20 patients with severe renal impairment (eGFR 20–30 ml/min per 1.73 m^2 at baseline) will be enrolled to provide additional pharmacokinetic and safety information but will not contribute to the main efficacy analyses. Key trial eligibility criteria are listed in Table 1.

Study Design

APPLAUSE-IgAN (ClinicalTrials.gov identifier: NCT04578834) is a global, randomized, double-blind, placebo-controlled, parallel-group, pivotal Phase 3 study (Figure 2). The trial is currently recruiting patients across >200 centers in 34 countries. The trial is designed and executed in accordance with the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Tripartite

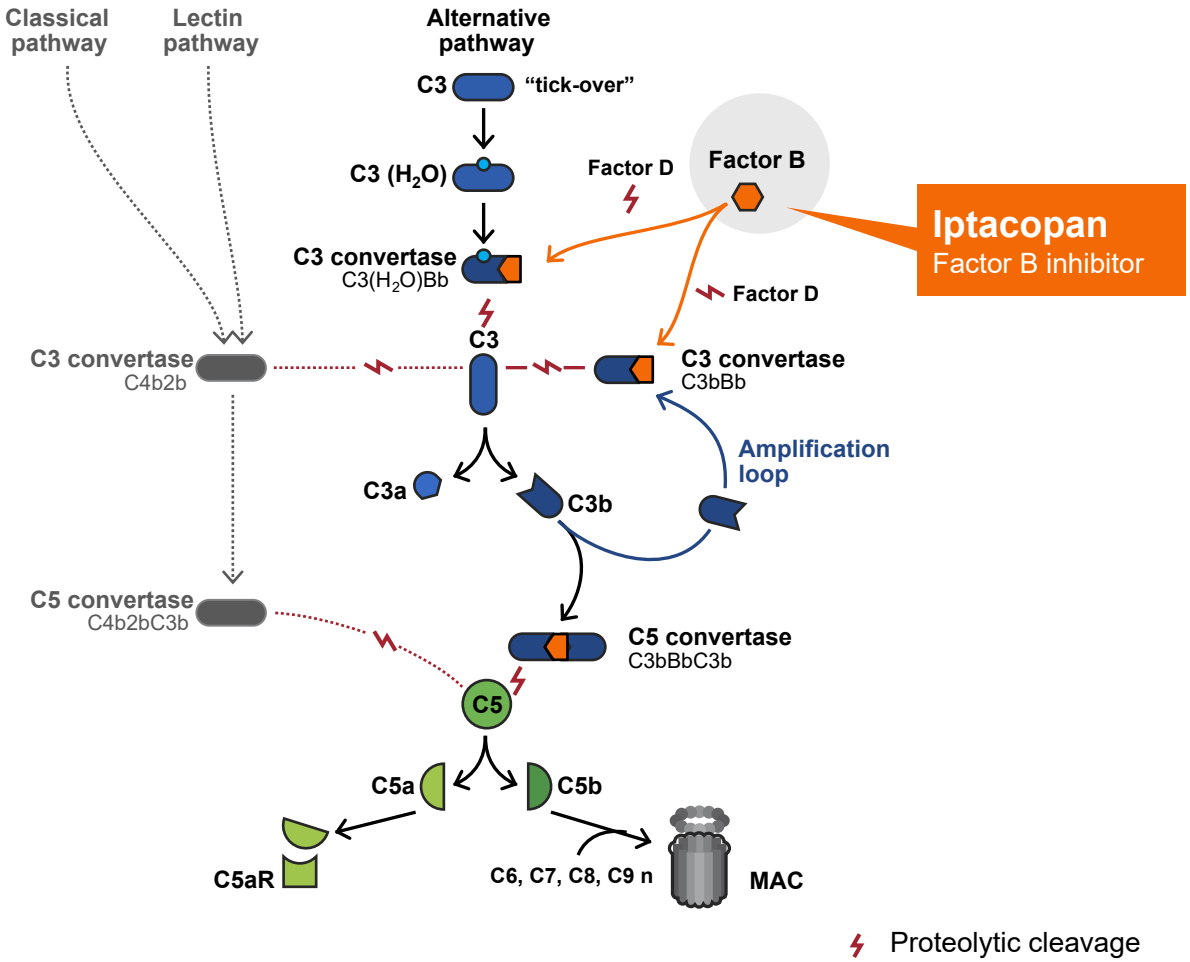

Figure 1. Iptacopan is a proximal complement inhibitor that specifically binds to FB to inhibit the activation of the AP and amplification loop. AP, alternative pathway; FB, Factor B; MAC, membrane attack complex.

Guidelines [ICH E6(R2) Integrated Addendum] for Good Clinical Practice and will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. All participants will provide written informed consent before enrollment.

The study comprises a screening visit, a run-in period of up to 3 months, and a 24-month treatment period (Figure 2). As is typical of IgAN clinical trials, the run-in period is used for stabilization of background therapy with an ACEi or ARB at a maximally

Table 1. Key inclusion and exclusion criteria[a]

Inclusion criteria	Exclusion criteria
• Aged ≥18 yr with eGFR ≥30 ml/min/1.73 m^2 and biopsy-confirmed IgAN[b] • Proteinuria (UPCR ≥ 1 g/g [113 mg/mmol]) at screening and completion of the run-in period • On supportive care, including locally approved maximal daily dose or maximally tolerated stable dose of ACEi/ARB for ≥90 d before study treatment. If taking diuretics, antihypertensive medication, or other background medication for IgAN, doses should be stable for ≥90 d before study treatment[c] • Vaccination against *Neisseria meningitidis, Streptococcus pneumoniae,* and *Haemophilus influenzae* (according to local regulation)	• Any secondary IgAN • Significant urinary obstruction or difficulty voiding and urinary tract disorder other than IgAN at screening and randomization • Presence of RPGN (≥50% decline in eGFR within 3 mo before screening), nephrotic syndrome, or acute kidney injury • HIV, HBV, and HCV infection; past malignancy; major concurrent comorbidities; or liver injury • SBP > 140 mm Hg or DBP > 90 mm Hg at randomization • Previous treatment with immunosuppressive or immunomodulatory agents within 90 d before study treatment • Bacterial, viral, or fungal infection within 14 d before randomization • Prior transplantation (any solid organ transplantation) • Prior use of iptacopan or participation in any other clinical trial of iptacopan

ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; IgAN, immunoglobulin A nephropathy; RPGN, rapidly progressive glomerulonephritis; SBP, systolic blood pressure; SGLT2I, sodium glucose transporter inhibitor; UPCR, urine protein-to-creatinine ratio.
[a]Eligibility criteria presented refer to the main cohort only.
[b]eGFR ≥ 45 ml/min per 1.73 m^2: biopsy within 5 yr; eGFR 30 to <45 ml/min per 1.73 m^2: biopsy within 2 yr with <50% tubulointerstitial fibrosis. The cohort of patients with severe renal impairment (not described here; eGFR 20 to <30 ml/min per 1.73 m^2) will not contribute to the main efficacy. Consequently, a qualifying biopsy to confirm IgAN diagnosis may be performed at any time for patients in this population.
[c]Including SGLT2i.

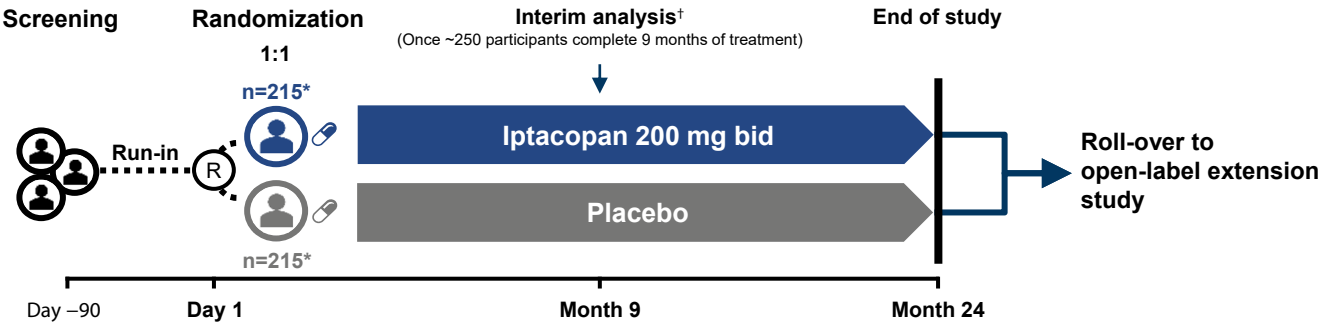

Figure 2. Study design of APPLAUSE-IgAN (NCT04578834). The asterisk (*) denotes the main population only; the population with severe renal impairment ($n \sim 20$) is not depicted. BID, twice daily; R, randomization.

approved or maximally tolerated dose. Patients receiving sodium/glucose cotransporter-2 (SGLT2) inhibitors as part of the background therapy must also be on stable dose (for 90 days) before initiation of the study treatment. At the end of the run-in period, eligible patients are randomized 1:1 via interactive response technology to receive either iptacopan 200 mg or placebo twice daily orally. The interactive response technology will assign a randomization number to each eligible study participant, which will be used to assign the study participant to a treatment arm using a validated automated system. The main study population is stratified based on prognostically relevant parameters, namely baseline UPCR, eGFR, and geographic region. After completing the 24-month treatment period, eligible patients have the option to enter a rollover extension study and receive open-label iptacopan (Figure 2).

Study Objectives and Clinical Questions of Interest

A prespecified IA will be performed when approximately 250 patients from the main study population complete the 9-month visit. The primary objective at the IA is to demonstrate the superiority of iptacopan over placebo on proteinuria reduction (assessed by UPCR sampled from a 24-hour urine collection) at 9 months. Following the IA, the study will continue in a blinded fashion until all patients have completed the 24-month treatment period with the primary objective of demonstrating superiority of iptacopan over placebo on slowing the rate of eGFR decline (total eGFR slope).

The study is designed to answer 2 primary clinical questions of interest:

The IA aims to answer what the treatment effect of iptacopan is versus placebo on proteinuria reduction, without confounding because of initiation of other IgAN treatments or kidney replacement therapy post-randomization expected to happen more often in the placebo arm. Such IgAN treatments include corticosteroids or immunosuppressants, other newly approved drugs (e.g., delayed-release budesonide), or background medications (e.g., SGLT2 inhibitors). The initiation of other treatments for IgAN during the study or kidney replacement therapy are considered as "intercurrent events" (events occurring after treatment initiation that affect either the interpretation or the existence of values relevant for answering the clinical question of interest)[24,25] and will be handled by the "hypothetical strategy" outlined in the ICH E9 (R1) guidance.[25] This means that values following initiation of these treatments or kidney replacement therapy will be imputed so as to reflect that their occurrence likely indicates disease worsening.[25] Participants who discontinue treatment will continue to be followed and their data collected after treatment discontinuation would be used to estimate the treatment effect, according to the intention-to-treat principle.

The final analysis aims to establish the treatment effect of iptacopan versus placebo on the rate of eGFR decline. Similar to the IA, it is of clinical interest to evaluate the treatment effect without confounding because of initiation of other IgAN treatments but including all data for patients who discontinued treatment.

The key study objectives and end points of the IA and final analysis are summarized in Tables 2 and 3, respectively. In addition to clinical outcomes, the study will evaluate a panel of patient-reported outcomes, including Functional Assessment of Chronic Illness Therapy–Fatigue. Changes in plasma and urine biomarkers that reflect complement activation, inflammation, kidney damage, and the effect of iptacopan treatment at 9 and 24 months will also be evaluated (Tables 2 and 3).

Safety

Safety data (AEs, deaths, vital signs [particularly systolic and diastolic blood pressure], and laboratory data) will be collected throughout the study. An independent data monitoring committee will periodically evaluate safety data throughout the study.

Table 2. Primary and key secondary objectives and end points at interim analysis

Objective	End point
Primary objective	Primary end point
• To demonstrate the superiority of iptacopan vs. placebo in reducing proteinuria at 9 mo by measuring UPCR sampled from a 24-h urine collection[a]	• Log-transformed ratio to baseline in UPCR (sampled from a 24-h urine collection) at 9 mo
Secondary objectives	Secondary end points
• To demonstrate superiority of iptacopan vs. placebo on slowing eGFR decrease as measured by the change from baseline in eGFR • To assess the effect of iptacopan vs. placebo on the proportion of study participants reaching proteinuria <1 g/g of UPCR (sampled from a 24-h urine collection) at 9 mo	• Change from baseline in eGFR at 9 mo • Proportion of participants reaching UPCR <1 g/g (sampled from a 24-h urine collection) at 9 mo, without receiving corticosteroids/immunosuppressants or other newly approved drugs or kidney replacement therapy, or initiating new background therapy, for the treatment of IgAN
• To evaluate the effect of iptacopan vs. placebo on slowing IgAN progression as measured by the annualized total slope of eGFR decline over 1 yr	• Annualized total eGFR slope estimated over 12 mo
• To assess the effect of iptacopan vs. placebo on the change from baseline to 9 mo in fatigue scale as measured by the FACIT-Fatigue questionnaire	• Change from baseline to 9 mo in the fatigue scale as measured by the FACIT-Fatigue questionnaire
• To evaluate the safety and tolerability of iptacopan in comparison with placebo	• Safety end points (including adverse events/serious adverse events, safety laboratory parameters, vital signs) collected from baseline to 9 mo
Exploratory objectives	Exploratory end points
• To evaluate the effect of iptacopan vs. placebo on the change from baseline in measures of HRQoL	• Change from baseline to 9 mo in measures of HRQoL
• To explore the utility of blood and/or urine biomarkers related to treatment effect with iptacopan	• Selected blood and/or urine biomarkers related to disease progression and iptacopan treatment at 9 mo

eGFR, estimated glomerular filtration rate; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; IgAN, immunoglobulin A nephropathy; UPCR, urine protein-to-creatinine ratio.
[a]If the primary objective (proteinuria reduction) at interim analysis does not meet statistical significance, this objective would be re-evaluated as a secondary objective at the final analysis in all participants.

Statistical Analysis

The hypotheses related to the primary clinical questions of interest at the IA and final analysis, as well as selected key secondary hypotheses, are planned to be tested for superiority of iptacopan over placebo. The sequentially rejective multiple test procedures will be used for testing to control the study-wise type 1 error for multiplicity of testing at one-sided 2.5%.[26]

At the IA, the primary end point will be assessed by a mixed model for repeated measures for the log ratio to

Table 3. Primary and secondary objectives and end points at study completion

Objective	End point
Primary objective	Primary end point
• To demonstrate the superiority of iptacopan vs. placebo in slowing IgAN progression as measured by the annualized total slope of eGFR decline over 24 mo	• Annualized total eGFR slope estimated over 24 mo
Secondary objectives	Secondary end points
• To demonstrate the superiority of iptacopan vs. placebo on delaying the time to first occurrence of a composite kidney failure end point	• Time from randomization to first occurrence of a composite kidney failure end point event, defined as reaching: ○ Sustained ≥30% decline in eGFR relative to baseline, or ○ Sustained eGFR <15 ml/min/1.73 m^2 or ○ Maintenance dialysis, or ○ Receipt of kidney transplant, or ○ Death from kidney failure
• To demonstrate the superiority of iptacopan vs. placebo on the proportion of study participants reaching proteinuria <1 g/g of UPCR (sampled from a 24-h urine collection) at 9 mo	• Proportion of participants reaching UPCR (sampled from a 24-h urine collection) <1 g/g at 9 mo without receiving corticosteroids/immunosuppressants or other newly approved drugs, or initiating new background therapy for the treatment of IgAN, or initiating kidney replacement therapy
• To demonstrate the superiority of iptacopan vs. placebo on the change from baseline to 9 mo in the fatigue scale as measured by the FACIT-Fatigue questionnaire	• Change from baseline to 9 mo in the fatigue scale as measured by the FACIT-Fatigue questionnaire
• To evaluate the safety and tolerability of iptacopan	• Safety end points (including AEs/SAEs, safety laboratory parameters, vital signs) collected from baseline to 9 mo
Exploratory objectives	Exploratory end points
• To evaluate the effect of iptacopan vs. placebo on the change from baseline in measures of HRQoL	• Change from baseline to 9 and 24 mo in measures of HRQoL • Change from baseline to 24 mo in the fatigue scale measured by the FACIT-Fatigue questionnaire
• To explore the utility of blood and/or urine biomarkers related to treatment effect with iptacopan	• Selected blood and/or urine biomarkers related to disease progression and iptacopan treatment at 9 and 24 mo

AE, adverse event; eGFR, estimated glomerular filtration rate; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; IgAN, immunoglobulin A nephropathy; SAE, serious AE; UPCR, urine protein-to-creatinine ratio.

baseline in 24-hour UPCR. Values collected after intercurrent events handled with the hypothetical strategy will be imputed via a modeling approach accounting for their occurrence as potentially indicative of a worsening condition (see Supplementary Materials for additional details). Patients discontinuing treatment will continue to be followed and their data will be included in the analysis, as per the intention-to-treat principle.

At the final analysis, the primary end point will be assessed using a longitudinal mixed effects model for eGFR. Measurements after intercurrent events will be handled following the same principles described for the IA.

Additional sensitivity analyses considering alternative approaches to handle or impute values after an intercurrent event are also planned to confirm the consistency of treatment effects across different modeling assumptions.

Sample Size Estimation

Assuming a 25% to 30% reduction in UPCR and a standard deviation (SD) of 0.7 (on the log scale), a sample size of 250 patients provides 75% to 92% power for the primary analysis at the IA. Assuming a difference of 1.1 ml/min per 1.73 m^2 and an SD of 3.5 in annualized total eGFR slope over 2 years, a sample size of approximately 430 patients provides approximately 90% power at a one-sided significance level of 0.025 for the primary analysis at the final analysis.

DISCUSSION

Despite advances in our understanding of the pathogenesis of IgAN, until recently there had been no disease-specific therapies for patients with IgAN and there is still a large unmet need for safe, well-tolerated, and efficacious novel therapies that specifically target pathogenic pathways of kidney damage in IgAN.

IgAN is an infrequent, heterogeneous, progressive disease with few disease-specific symptoms that frequently remains undiagnosed until substantial loss of kidney function has occurred. Thus, clinical research to evaluate the benefits of an early intervention is challenging because of the long follow-up times required for "hard" clinical end points.[27] The National Kidney Foundation, in collaboration with the US Food and Drug Administration and the European Medicines Agency, recently led a scientific workshop to evaluate candidate surrogate end points in chronic kidney disease, including IgAN.[28,29] Based on meta-analyses of randomized and observational studies, and computer simulations conducted as part of this scientific effort, eGFR slope (rate of eGFR decline) was validated as a surrogate end point for kidney outcomes that could therefore be used for confirmatory assessment of treatment benefit.[29] Similarly, based on the existing evidence, the US Kidney Health Initiative supported the use of proteinuria reduction as a reasonably likely surrogate end point predictive of long-term benefit in kidney outcomes in patients with IgAN.[28] A meta-analysis of 12 randomized controlled trials in the IgAN population suggested that approximately 30% reduction in proteinuria would confer treatment benefits on eGFR slope with very high probability[30,31] confirming the association between proteinuria and eGFR slope and thus supporting the rationale for using these end points in IgAN trials.[30] Consequently, trial designs have been proposed where the treatment effect on early proteinuria reduction is evaluated at an IA to support accelerated approval, and the long-term effects on eGFR slope are evaluated at study completion.[29,30,32] Delayed-release budesonide targeting intestinal mucosal tissue, where IgAN is thought to originate, is the first drug to receive accelerated approval for IgAN treatment based on proteinuria reduction, while data on its effects on eGFR are expected.[11–13] Such novel, more efficient trial designs are beneficial not only from the drug development perspective but also from a patient and caregiver perspective because they enable earlier access to more efficacious treatments to slow or prevent irreversible histopathologic damage. Several ongoing Phase 3 trials evaluating drugs that target pathogenic pathways in IgAN are using similar design approaches[32] (Table 4[33–38]). APPLAUSE-IgAN is one of the largest randomized controlled trials in IgAN, adopting this novel design approach with early proteinuria reduction evaluated as a primary end point in an IA, and the difference in annualized eGFR slope over 24 months is evaluated as a primary end point at study completion.

Importantly, IgAN not only results in progressive kidney function decline necessitating need for dialysis and/or kidney transplant that are associated with significant reduction in life expectancy, but also adversely affects the QoL and psychosocial well-being of patients.[39,40] Reduced life participation and ability to work, fatigue, depression, and fear of relapse are identified as major concerns by patients with glomerular disease, including IgAN, as well as their caregivers. Fatigue and anxiety or depression were ranked as having a high impact on their daily lives,[39,40] and some patients attribute high value to treatments that can lead to short-term improvements in QoL.[41] Evaluating patient-centric outcomes increases patient involvement and provides evidence of the holistic benefits of a therapy, facilitating future treatment decisions. However, such end points are infrequently assessed in randomized controlled trials of glomerular diseases.[27,39] At the time of writing this, APPLAUSE-IgAN is the only ongoing Phase 3 IgAN trial that incorporates the impact

Table 4. Salient features of key ongoing Phase 3 randomized trials in IgAN

Study characteristics	APPLAUSE-IgAN[33] (iptacopan) NCT04578834	ARTEMIS-IGAN[34] (narsoplimab) NCT03608033	PROTECT[35] (sparsentan) NCT03762850	ALIGN[36] (atrasentan) NCT04573478	NefIgArd[37] (budesonide) NCT03643965	VISIONARY[38] (sibeprenlimab) NCT05248646
MoA	Factor B inhibitor	MAb against MASP2	Dual-acting ARB and endothelin receptor antagonist	Endothelin A receptor inhibitor	Steroid	Humanized IgG2 monoclonal antibody against APRIL
Study design	Multicenter, randomized (1:1), double-blind, placebo-controlled study	Multicenter, double-blind, randomized (1:1), placebo-controlled study	Randomized (1:1), multicenter, double-blind, parallel-group, active-control study	Randomized (1:1), multicenter, double-blind, placebo-controlled study	Randomized (1:1), multicenter, double-blind, placebo-controlled study	Randomized (1:1), multicenter, double-blind, placebo-controlled study
Comparator	Placebo	Placebo	Irbesartan	Placebo	Placebo	Placebo
Patients	Adult patients ($N = 450$[a]) with biopsy-proven primary IgAN, proteinuria ≥ 1 g/g, despite optimal RAS blockade and eGFR ≥ 30 ml/min/1.73 m^2	Adult patients ($N = 450$) with biopsy-proven primary IgAN, proteinuria > 1 g/d (6 mo before screening) or UPCR > 0.75 g at screening, and eGFR ≥ 30 ml/min/1.73 m^2	Adult patients ($N = 380$) with biopsy-proven primary IgAN, proteinuria ≥ 1 g/d, on stable, maximally tolerated dose of ACEi/ARB, and eGFR ≥ 30 ml/min/1.73 m^2	Patients ($N = 380$) with biopsy-proven primary IgAN, urine protein ≥ 1 g/d, on maximally tolerated, stable dose of ACEi/ARB[c] and eGFR ≥ 30 ml/min/1.73 m^2. Patients in the SGLT2i stable stratum must be on stable dose of an SGLT2i for ≥12 wk before screening (as per investigator choice) in addition to maximally tolerated and optimized dose of RAS inhibitor that has been stable for ≥12 wk before screening	Adult ($N = 365$) patients with biopsy-proven primary IgAN, UPCR ≥ 1 g/24 h, on stable and maximum dose of RAS inhibitor therapy and eGFR ≥ 35 ml/min/1.73 m^2 and ≤90 ml/min/1.73 m^2	Adult patients ($N = 470$[b]) with biopsy-proven IgAN, UPCR ≥ 0.75 g/g or urine protein ≥ 1.0 g/d, eGFR ≥ 30 ml/min/1.73 m^2, and on stable and maximally tolerated dose of ACEi/ARB[c]; patients on stable dose of SGLT2i if initiated ≥3 mo before screening
Includes patients from Asia	Yes	No	Yes	Yes	Yes	NA
Primary outcome(s)	• Log-transformed ratio to baseline in UPCR (sampled from a 24-h urine collection) at 9 mo (interim analysis) • Annualized total eGFR slope estimated over 24 mo (at study completion)	• Change from baseline in 24-h UPE at wk 36	• Change from baseline in UPCR at wk 36	• Change from baseline in UPCR at wk 24	• Change from baseline in UPCR at mo 9 • Change from baseline in eGFR	• Change from baseline in 24-h UPCR at mo 9
Key secondary efficacy outcomes	• Time from randomization to first occurrence of a composite kidney failure end point event: (≥30% decline in eGFR, eGFR < 15 ml/min/1.73 m^2, maintenance dialysis, kidney transplant, or death from kidney failure) • Proportion of participants reaching UPCR (sampled from a 24-h urine collection) <1 g/g at 9 mo • Change from baseline to 9 mo in the fatigue scale as measured by the FACIT-Fatigue questionnaire	• Change from baseline in renal function as determined by the rate of change in eGFR up to 144 wk • Change from baseline in 24-h UPE at 36 wk in the subset of patients with high baseline proteinuria (defined as 24-h UPE ≥ 2 g/d) • Time-averaged change in UPCR to 36 wk	• Rate of change in eGFR over 52-, 104-, and 110-wk period	• Change from baseline in eGFR at the end of study • Proportion of patients in the non-SGLT2i stratum experiencing ≥30% reduction in eGFR or eGFR < 15 ml/min/1.73 m^2 or chronic dialysis, sustained for ≥30 d, or kidney transplantation or all-cause mortality • Proportion of patients experiencing ≥40% reduction in eGFR or eGFR < 15 ml/min/1.73 m^2 or chronic dialysis for ≥30 d or kidney transplantation or all-cause mortality	• Kidney function as measured by eGFR using CKD-EPI formula	• Annualized rate of change from baseline (slope) of eGFR over 24 mo • Proportion of patients achieving urine total protein < 1.0 g/d and ≥25% reduction from baseline at 12 mo • Annualized slope of eGFR over 12 mo

ACEi, angiotensin-converting enzyme inhibitor; APRIL, a proliferation-inducing ligand; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FACIT, Functional Assessment of Chronic Illness Therapy; IgAN, immunoglobulin A nephropathy; mAb, monoclonal antibody; MASP2, mannose-binding lectin–associated serine protease 2; MoA, mechanism of action; *N*, total number of patients; RAS, renin-angiotensin system; TEAE, treatment-related adverse event; UPCR, urinary protein-to-creatinine ratio; UPE, urinary protein excretion.

[a]Including approximately 20 patients with severe renal impairment (eGFR 20 to <30 ml/min per 1.73 m^2) who will not be included in the main efficacy analyses.

[b]Including an exploratory cohort of 20 patients with eGFR 20 to <30 ml/min per 1.73 m^2.

[c]Patients unable to tolerate RAS inhibitors (ACEi/ARB) may also be enrolled.

of fatigue on QoL as a key secondary outcome, measured using the Functional Assessment of Chronic Illness Therapy–Fatigue tool.[42] In addition, other widely used patient-reported outcome measures are also being evaluated to get a holistic understanding of the benefit of iptacopan on patients' QoL. An optional patient interview will also be conducted to further understand the patients' experience of meaningful changes in their condition, as well as of the patient-reported outcome measures used in the study.

Clinical, pathologic, and genetic evidence has demonstrated the role of complement-pathway activation in IgAN pathogenesis and its association with worse kidney prognosis.[15] These insights have stimulated the development of an array of complement-pathway inhibitors targeting the AP, LP, and terminal pathway as potential therapies for IgAN.[8,43] Inhibition of the complement system, particularly its distal common steps by blocking C5 convertase, is associated with an increased risk of infection (particularly from *Neisseria* species) owing to insufficient membrane attack complex formation and downstream effects.[8] In contrast, iptacopan specifically targets upstream steps of AP activation but does not inhibit direct activation of the LP or CP and hence does not block the generation of membrane attack complex triggered by direct CP and/or LP activation.[18] Instead, iptacopan inhibits amplification of the initial complement response by CP or LP through AP, thus preventing overactivation of the complement system (Figure 1).[18] As a result, in vaccinated individuals, FB inhibition (with iptacopan) does not increase the susceptibility to meningococcal and pneumococcal infections.[44,45] Indeed, in recent Phase 2 trials of iptacopan in IgAN and C3 glomerulopathy, no serious infections suspected to be related to iptacopan and no dose-related increase in infection rate were reported during treatment.[20–23] Particularly in the IgAN Phase 2 study, most AEs were mild or moderate in severity with no deaths and treatment-emergent serious AEs in only 2 of 112 patients, both unrelated to study treatment.[19,20] Overall, iptacopan has showed a well-tolerated safety profile in the clinical studies so far, supporting its further evaluation.

FB is an AP-specific serine protease that complexes with C3b to drive the catalytic activity of the AP C3 and C5 convertases. Iptacopan binds to the catalytically active site of FB (in the Bb fragment) with an IC_{50} value of 0.01 ± 0.006 μM and demonstrates potent inhibition of AP-induced membrane attack complex formation (IC_{50} of 0.13 ± 0.06 μM). Iptacopan is also highly selective; no inhibition of factor D or CP or LP activation were observed (up to 100 μM) with iptacopan (Figure 1).[18] Therefore, iptacopan is expected to prevent pathologic drivers of IgAN from activating the AP and its amplification loop, both systemically and in the kidneys as demonstrated by biomarkers of complement activation in serum and urine in patients with IgAN[19,20] and reduction in C3 deposit scores in patients with recurrent C3 glomerulopathy following kidney transplantation.[46] Although there is strong evidence for the involvement of AP in IgAN pathogenesis, LP activation is also observed in some patients and correlates with poor outcomes. A Phase 3 trial is currently ongoing to evaluate the benefits of inhibiting LP activation with narsoplimab (a monoclonal antibody targeting mannose-binding lectin–associated serine protease 2) in patients with IgAN.[34] Although LP activation may drive IgAN pathogenesis in some patients, the amplification loop of the AP plays a pivotal role in amplifying the initial complement response, contributing nearly 80% of the downstream complement response,[8,47] thereby exacerbating complement-mediated kidney damage in IgAN. Although iptacopan does not inhibit LP directly, it blocks the amplification loop of the AP and is thus expected to attenuate LP activation, thereby limiting complement-mediated kidney injury. In the Phase 2 study, iptacopan treatment showed strong inhibition of AP and proteinuria reduction in patients with IgAN,[19] supporting its further evaluation in this population.

In view of the complexities and the unique challenges of evaluating anticomplement therapies, a workshop facilitated by the National Kidney Foundation has recommended a framework on various aspects of design and conduct of clinical trials evaluating complement inhibitors in glomerular diseases.[48] APPLAUSE-IgAN incorporates key elements proposed in this framework as essential to demonstrate conclusive clinical benefit and safety of anticomplement therapies, including, but not limited to, evaluating outcomes that are relevant to patients as well as strategies to mitigate the potential risks in patients treated with iptacopan.

Several other key features of APPLAUSE-IgAN merit further mention. This study includes a cohort of patients with severe renal impairment (eGFR 20–30 ml/min per 1.73 m^2), excluded from the vast majority of clinical trials. Although these patients will not be considered in the main efficacy analyses of APPLAUSE-IgAN, their inclusion will provide invaluable information on the safety of complement-inhibitor therapy, specifically iptacopan, in patients with advanced chronic kidney disease. The prevalence, clinical, and histopathologic patterns and treatment response of IgAN vary across different populations or ethnicities.[49] APPLAUSE-IgAN is a global trial recruiting patients from diverse geographies and ethnicities, including Asia, Europe, and America. The study design

incorporates several key aspects that are particularly relevant to IgAN, such as a run-in period of at least 90 days and rigorous requirements of supportive care with maximally tolerated and stable doses of ACEis/ARBs. This ensures that patients have derived maximal benefit from optimal supportive care and that no confounding of the study end points attributable to supportive care is expected. This is particularly relevant owing to criticism of outcomes from IgAN cohorts in trials enrolling a broader population of patients with chronic kidney disease,[50] in which supportive care was not necessarily optimized before the randomized treatment period and thus, potentially confounding the actual benefits derived from the pharmacologic intervention.[51]

The estimand framework, recommended by the recently updated ICH E9 guideline,[24,25] is fully implemented in the design of APPLAUSE-IgAN study. It is a systematic approach to comprehensively describe the clinical questions of interest a study aims to answer and to ensure alignment among the study's objectives, trial execution or conduct, statistical analyses, and interpretation of results. This includes identifying "intercurrent events," events which may occur postrandomization (e.g., initiation of symptomatic treatment) and affect the interpretation of the treatment effect of interest, and clearly articulating how these will be handled in the analyses.[24,25] Following this approach, the study protocol clearly defines how intercurrent events (such as treatment discontinuations, initiation of corticosteroids or immunosuppressants) will be dealt with, which not only ensures that the data needed to address specific scientific questions of interest are collected but also that the appropriate statistical methods are prespecified. This adds precision to the study design and ensures that the questions of interest are answered as transparently and accurately as possible.

In conclusion, the APPLAUSE-IgAN study incorporates learnings from past studies in chronic kidney disease and IgAN, in addition to key recommendations emerging from leading initiatives of the US Kidney Health Initiative, National Kidney Foundation, and regulatory agencies. Along with clinically relevant outcomes, the study also incorporates patient-centric outcomes that evaluate patients' QoL, in alignment with various initiatives, such as Standardized Outcomes in Nephrology–Glomerular Disease and National Kidney Foundation. Iptacopan is a promising, oral, small-molecule targeted therapy that by inhibiting AP activation has the potential to reduce inflammatory damage in kidneys to slow or prevent IgAN progression in a tailored approach, while minimizing risks associated with the use of traditional immunosuppressive therapies.

DISCLOSURE

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AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study, drafting, and critical review of the manuscript. OP contributed to the development of statistical analysis plan for the study. All authors have read and approved the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods (Statistical Analysis).

CONSORT Checklist.

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