ORIGINAL ARTICLE

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

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ABSTRACT

BACKGROUND

The alternative complement pathway plays a key role in the pathogenesis of IgA nephropathy. Iptacopan specifically binds to factor B and inhibits the alternative pathway.

METHODS

In this phase 3, double-blind, randomized, placebo-controlled trial, we enrolled adults with biopsy-confirmed IgA nephropathy and proteinuria (defined as a 24-hour urinary protein-to-creatinine ratio of ≥1 [with protein and creatinine both measured in grams]) despite optimized supportive therapy. Patients were randomly assigned, in a 1:1 ratio, to receive oral iptacopan (200 mg) or placebo twice daily for 24 months while continuing to receive supportive therapy. The primary objective of this prespecified interim analysis was to assess the efficacy of iptacopan as compared with that of placebo in reducing proteinuria at month 9; the primary end point was the change from baseline in the 24-hour urinary protein-to-creatinine ratio at month 9. The proportion of patients who had a 24-hour urinary protein-to-creatinine ratio of less than 1 at month 9 without receiving rescue or alternative medication or undergoing kidney-replacement therapy (dialysis or transplantation) was a secondary end point. Safety was also assessed. The effect of iptacopan on kidney function will be assessed at the end of the 2-year double-blind treatment period.

RESULTS

The main trial population included 222 patients in the iptacopan group and 221 in the placebo group. The interim efficacy analysis included the first 250 patients who underwent randomization in the main trial population (125 patients in each group) and who remained in the trial until month 9 or discontinued the trial by month 9. Safety was assessed in all the patients in the main trial population. At month 9, the adjusted geometric mean 24-hour urinary protein-to-creatinine ratio was 38.3% (95% confidence interval, 26.0 to 48.6; two-sided P<0.001) lower with iptacopan than with placebo. The reduction in proteinuria was supported by consistent results in secondary end point analyses. There were no unexpected safety findings with iptacopan. The incidence of adverse events that occurred during the treatment period was similar in the two groups; most events were mild to moderate in severity and reversible. No increased risk of infection was observed.

CONCLUSIONS

Among patients with IgA nephropathy, treatment with iptacopan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo. (Funded by Novartis; APPLAUSE-IgAN ClinicalTrials.gov number, NCT04578834.)

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*A complete list of the APPLAUSE-IgAN Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 25, 2024, and updated on November 7, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2410316

IgA nephropathy is the most prevalent type of glomerulonephritis worldwide, affecting approximately 2.5 per 100,000 persons per year.[1] The incidence varies according to geographic region and is higher in East Asia than in other areas of the world.[1-8] IgA nephropathy is typically seen in young or middle-aged adults and leads to progressive loss of kidney function in most patients, particularly those with elevated urinary protein excretion.[9,10] Thus, it is a frequent cause of kidney failure.[7,11] Recent advances have highlighted the immunologic basis of IgA nephropathy. Immune complexes containing galactose-deficient IgA1 accumulate in the glomerular mesangium, triggering local inflammation, scarring, and kidney damage.[12-18] The presence of complement proteins in the glomeruli of patients with IgA nephropathy has long been noted, and multiple studies support the involvement of the alternative complement pathway.[12,14,16-18] Interventions for IgA nephropathy have historically focused on supportive treatment with renin–angiotensin system inhibitors,[11] with interventions for the underlying immune disorder limited to severe cases. Treatment of glomerular inflammation in patients with IgA nephropathy remains limited to glucocorticoids, which are associated with substantial adverse events.[19-23] A formulation of the oral glucocorticoid budesonide (Nefecon) — designed to specifically deliver drug to the distal small intestine, where it reduces production of pathogenic IgA by the mucosal immune system[24] — was recently approved for the treatment of IgA nephropathy.

Iptacopan (LNP023) is an oral, first-in-class, highly potent proximal complement inhibitor that specifically binds to factor B and inhibits the alternative pathway.[25,26] Factor B inhibition blocks the activity of alternative pathway–related C3 convertase, preventing downstream generation of alternative pathway C5 convertase and the formation of C3a and C5a anaphylatoxins and the membrane attack complex.[25] A phase 2 study involving patients with IgA nephropathy showed that iptacopan reduces proteinuria in a dose-dependent manner; biomarker data have confirmed the drug's mechanism of action.[27]

The current phase 3 trial (A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase III Study to Evaluate the Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients [APPLAUSE-IgAN]) is evaluating the effects of iptacopan on proteinuria and kidney function in patients with IgA nephropathy who are at risk of progression.[28] Here, we report the results of the prespecified interim analysis, which assessed the effects of iptacopan on proteinuria.

Methods

Trial Oversight and Design

This ongoing, phase 3, international, double-blind, randomized, placebo-controlled trial was overseen by an academic-led steering committee (a list of the members is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org), in partnership with the sponsor (Novartis). The sponsor was responsible for the trial design, conduct, and analysis. The steering committee provided leadership and scientific supervision, oversaw the trial design and conduct, and was responsible for reporting the results. The first author wrote the first draft of the manuscript, and all the authors contributed to revisions. All the authors had access to the data within the manuscript's scope, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol, available at NEJM.org. All the authors signed data confidentiality agreements. Editorial assistance was provided by a medical writer, funded by the sponsor, in accordance with Good Publication Practice guidelines. The trial was conducted in accordance with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. The trial was approved by relevant regulatory authorities, as well as institutional review boards at the participating centers. All the patients provided written informed consent before they underwent any trial-related procedures.

The trial design has been previously reported and is summarized in Figure S1 in the Supplementary Appendix.[28] After screening, patients entered a run-in period of up to 3 months, during which they received optimized supportive care. Those who met the eligibility criteria underwent randomization in a 1:1 ratio and were assigned to receive oral iptacopan (at a dose of 200 mg) twice daily or matching placebo, in addition to optimized supportive care. Randomization was stratified according to geographic region (Asia vs.

all other regions), baseline proteinuria (24-hour urinary protein-to-creatinine ratio [with protein and creatinine both measured in grams] of <2 vs. ≥2), and estimated glomerular filtration rate (eGFR; 30 to <45 ml per minute per 1.73 m^2 of body-surface area vs. ≥45 ml per minute per 1.73 m^2).

PATIENTS

Patients were eligible for the trial if they had primary IgA nephropathy confirmed by biopsy within the previous 5 years (for patients with an eGFR of ≥45 ml per minute per 1.73 m^2) or within 2 years if the biopsy showed less than 50% tubulointerstitial fibrosis (for patients with an eGFR of 30 to <45 ml per minute per 1.73 m^2), and if they had a baseline 24-hour urinary protein-to-creatinine ratio of at least 1 despite optimized supportive care. Patients who met these criteria were included in the main trial population. An additional enrolled patient population with a baseline eGFR of 20 to less than 30 ml per minute per 1.73 m^2 will be assessed in the ongoing trial. Key inclusion and exclusion criteria are provided in the Supplementary Appendix.[28] Vaccinations against *Neisseria meningitidis* and *Streptococcus pneumoniae* were required, and vaccinations against *Haemophilus influenzae* type B were performed according to local availability and regulations. Vaccination recommendations were made in light of the known increased risk of serious encapsulated bacterial infections associated with the use of complement inhibitors.

TRIAL ASSESSMENTS AND ANALYSES

The primary end point was the change from baseline in the 24-hour urinary protein-to-creatinine ratio at month 9. The proportion of patients who had a 24-hour urinary protein-to-creatinine ratio of less than 1 at month 9 without receiving rescue or alternative medication or undergoing kidney-replacement therapy (dialysis or transplantation) was a secondary end point. Exploratory end points were the reduction in the 24-hour urinary albumin-to-creatinine ratio, total 24-hour urinary protein level, and total 24-hour urinary albumin level at month 9. Safety end points were also assessed. The protein-to-creatinine ratio from the first morning urine sample, hematuria, complement biomarkers, and patient-reported fatigue (as assessed with the Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-Fatigue] score) were also assessed (see the Supplementary Appendix). The effects on the eGFR are not reported in this interim analysis, and the data remain blinded to ensure trial integrity, as advised by regulatory agencies. The conduct of the interim analysis is described in the Supplementary Appendix.

STATISTICAL ANALYSIS

For the assessment of the primary end point at the time of the interim analysis, we calculated that a sample of 250 patients would provide the trial with 75 to 92% power, at a two-sided alpha of 1%, to show superiority of iptacopan over placebo in reducing the 24-hour urinary protein-to-creatinine ratio, assuming that the ratio would be 25 to 30% lower in the iptacopan group than in the placebo group, with a standard deviation of 0.7 (on the log scale).[28] The efficacy analyses included the first 250 patients in the main trial population who had undergone randomization and had completed the month 9 visit or discontinued the trial by month 9 as of the data-cutoff date for the interim analysis. Patients who had undergone randomization in error and never received iptacopan or placebo were excluded. Safety was assessed in all the patients in the main trial population who had received at least one dose of iptacopan or placebo by the data-cutoff date for the interim analysis (see the Supplementary Appendix).

The primary end point — the log-transformed change from baseline in the 24-hour urinary protein-to-creatinine ratio at month 9 — was analyzed with the use of a repeated-measures model. All the data recorded from baseline up to the month 9 visit, or to initiation of rescue or alternative medication or kidney-replacement therapy, were included in the analysis. Data collected after initiation of rescue or alternative medication or kidney-replacement therapy were not used and were instead imputed with values that reflected that initiation of these medications (or kidney-replacement therapy) most likely indicates worsening of disease. Data for patients who discontinued iptacopan or placebo were collected after discontinuation and were used in the analysis (see the Supplementary Appendix). A supplementary analysis was performed that included all values, regardless of whether these were collected after initiation of rescue or alternative medication (according to the intention-to-treat principle or

the treatment policy strategy). The proportions of patients who had a 24-hour urinary protein-to-creatinine ratio of less than 1 or less than 0.5 without receiving rescue or alternative medication or undergoing kidney-replacement therapy at month 9 were assessed separately with the use of a logistic-regression model (see the Supplementary Appendix). The consistency of treatment effect with respect to the primary end point was evaluated across subgroups defined according to sex, geographic region, baseline 24-hour urinary protein-to-creatinine ratio and eGFR, hematuria, baseline sodium–glucose cotransporter 2 (SGLT2) inhibitor use, and Oxford Classification MEST-C scores from qualifying biopsies.

To ensure strong control of the familywise type 1 error for multiplicity of testing to 5% (two-sided), the sequentially rejective multiple test procedures were used.[29] An alpha of 1% was allocated to test the primary end point at the interim analysis, and 4% was allocated to test the primary and secondary end points at the final analysis. Additional details are provided in the protocol. The results of secondary, exploratory, and post hoc analyses are reported with 95% confidence intervals but were not adjusted for multiplicity and therefore should not be interpreted as hypothesis tests. Safety data were summarized descriptively.

RESULTS

PATIENTS

From January 2021 to the data-cutoff date for the interim analysis (August 15, 2023), 1188 patients were screened, and 621 entered the run-in period. Of these, 443 patients from 164 sites in 34 countries underwent randomization in the main trial population (Fig. S2). The interim efficacy analyses included 250 patients from the main trial population (Fig. 1). The baseline characteristics of these 250 patients (Table 1) and the 443 patients included in the safety analysis (Table S1) were balanced between the two trial groups. The average age of the patients was 39 years, 47.6% were women, and 51.2% were from Asia. The mean (±SD) eGFR was 62.7±26.0 ml per minute per 1.73 m^2 in the iptacopan group and 65.5±26.7 ml per minute per 1.73 m^2 in the placebo group. The median 24-hour urinary protein-to-creatinine ratio was 1.81 (interquartile range, 1.36 to 2.66) in the iptacopan group and 1.87 (interquartile range, 1.48 to 2.83) in the placebo group. At baseline, 12.8% of the patients were taking SGLT2 inhibitors at a stable dose; the percentage of patients taking these agents was similar in the two trial groups. More than 99% of the patients were taking angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) at baseline. The median time from the qualifying biopsy to baseline was 1.3 years in the iptacopan group and 0.8 years in the placebo group. The trial population is broadly representative of patients with IgA nephropathy who are at risk of disease progression (Table S2).

At the time of data cutoff for the interim analysis, fewer patients in the iptacopan group than in the placebo group had discontinued the trial regimen (16.0% vs. 28.0%); the most frequent reason for discontinuation was meeting the criteria of the composite kidney end point (Fig. 1). Initiation of rescue or alternative medication by month 9 occurred in 2 patients (1.6%) in the iptacopan group and in 10 (8.0%) in the placebo group; included are patients who initiated glucocorticoids or other immunosuppressants (7 patients, all in the placebo group) or SGLT2 inhibitors (1 in the iptacopan group and 3 in placebo group) for the treatment of IgA nephropathy. By month 9, no patients in the iptacopan group and 2 patients in the placebo group had initiated dialysis.

EFFECT ON PROTEINURIA

The results of the primary analysis showed that iptacopan was superior to placebo in reducing the 24-hour urinary protein-to-creatinine ratio. At 9 months, the adjusted geometric mean 24-hour urinary protein-to-creatinine ratio was 38.3% (95% confidence interval [CI], 26.0 to 48.6) lower in the iptacopan group than in the placebo group (adjusted geometric mean, 0.562 in the iptacopan group and 0.910 in the placebo group; geometric mean ratio, 0.617; 95% CI, 0.514 to 0.740; two-sided P<0.001) (Fig. 2A). At 9 months, the adjusted geometric mean protein-to-creatinine ratio based on the first morning urine sample was 35.8% (95% CI, 22.6 to 46.7) lower in the iptacopan group than in the placebo group (Fig. 2B). This finding is consistent with that of the primary analysis of the 24-hour urinary protein-to-creatinine ratio (the median values over time are provided in Fig. S3). The results of the analyses of reductions in 24-hour urinary albumin-to-creat-

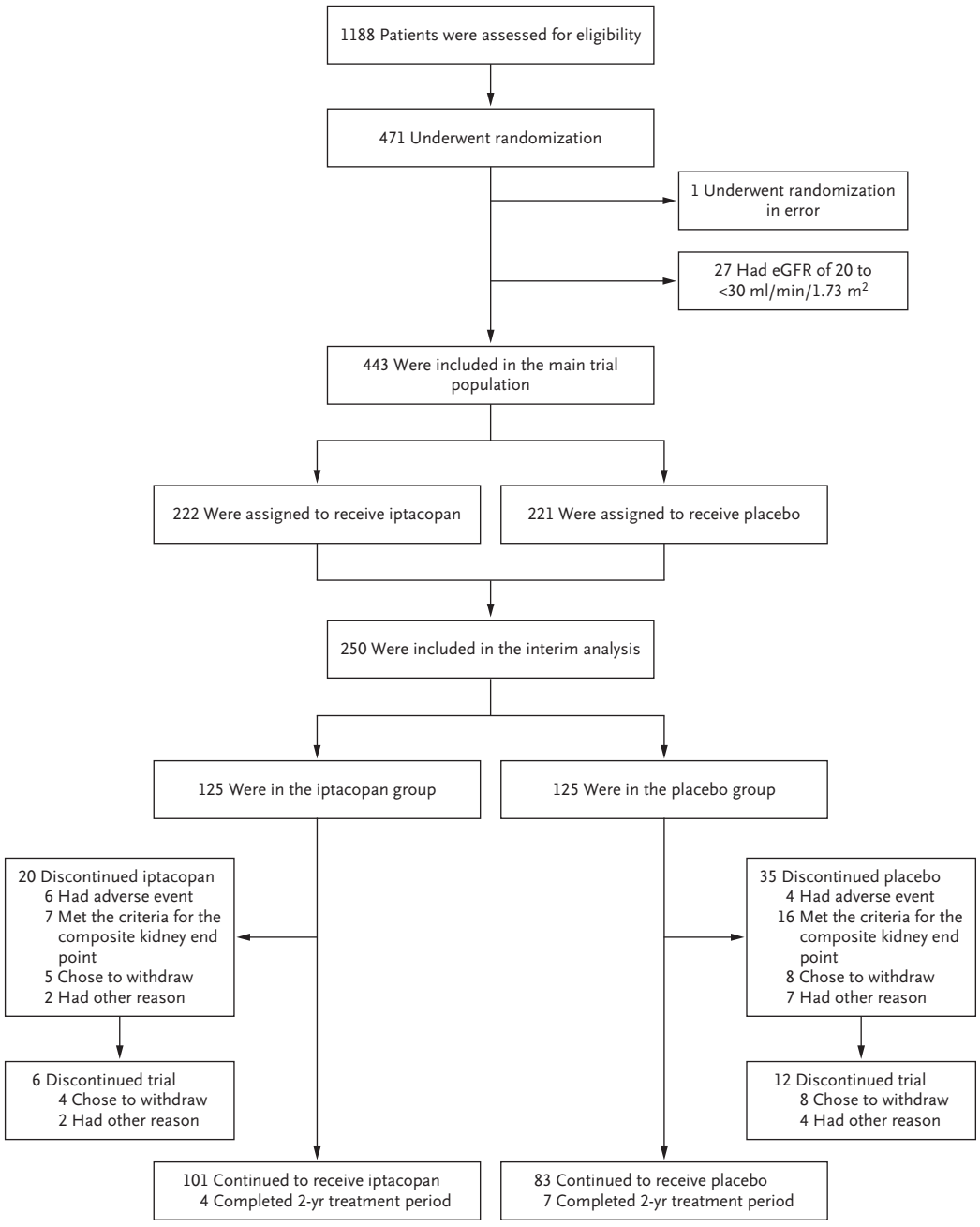

Figure 1. Screening, Randomization, and Follow-up.

Shown are the events that occurred up to the data-cutoff date for the interim analysis. The efficacy analyses included the first 250 patients who had undergone randomization in the main trial population and completed the month 9 visit or had discontinued the trial by month 9. Safety was assessed in the 443 patients in the main trial population. Only the most frequent reasons for discontinuation are reported; the other reasons are not reported in order to conceal the trial-group assignment of the patients in the ongoing double-blind trial. The composite kidney end point was a sustained decline in the estimated glomerular filtration rate (eGFR) of 30% or more from baseline over at least 4 weeks, a sustained eGFR of less than 15 ml per minute per 1.73 m^2 of body-surface area over a period of at least 4 weeks, maintenance dialysis (defined as dialysis for a period of ≥4 weeks), receipt of a kidney transplant, or death from kidney failure.[30] Adapted with permission from Perkovic et al.[31]

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Iptacopan (N=125)	Placebo (N=125)
Age — yr	39.3±12.4	39.6±12.6
Sex — no. (%)		
Female	54 (43.2)	65 (52.0)
Male	71 (56.8)	60 (48.0)
Geographic region — no. (%)		
Asia†	64 (51.2)	64 (51.2)
All other regions	61 (48.8)	61 (48.8)
Time since kidney biopsy — yr		
Mean	1.7±1.4	1.6±1.7
Median (IQR)	1.3 (0.5–2.8)	0.8 (0.3–2.6)
Oxford Classification MEST-C score — %‡		
M score		
M1	60.8	64.0
M0	32.0	31.2
E score		
E1	28.8	28.8
E0	63.2	64.8
S score		
S1	69.6	71.2
S0	22.4	23.2
T score		
T1 or T2	38.4	42.4
T0	54.4	53.6
C score		
C1	26.4	16.0
C2	1.6	1.6
C0	60.8	68.0
24-Hour urinary protein-to-creatinine ratio — g of protein/g of creatinine		
Median (IQR)	1.8 (1.4–2.7)	1.9 (1.5–2.8)
<2 — no. (%)	71 (56.8)	67 (53.6)
≥2 — no. (%)	54 (43.2)	58 (46.4)
eGFR — ml/min/1.73 m^2	62.7±26.0	65.5±26.7
eGFR distribution — no. (%)		
30 to <45	36 (28.8)	34 (27.2)
45 to <60	35 (28.0)	25 (20.0)
60 to <90	32 (25.6)	43 (34.4)
≥90	22 (17.6)	23 (18.4)
ACE inhibitor or ARB use at baseline — %§	>98%¶	>98%¶
≥50% maximal dose — no. (%)	101 (80.8)	99 (79.2)
≥80% maximal dose — no. (%)	64 (51.2)	69 (55.2)

Table 1. (Continued.)

Characteristic	Iptacopan (N=125)	Placebo (N=125)
Blood pressure — mm Hg‖		
Systolic	121.9±10.7	122.6±10.8
Diastolic	77.7±8.1	78.3±8.8
SGLT2 inhibitor use at baseline — no. (%)	18 (14.4)	14 (11.2)
Hematuria at baseline — no. (%)**	97 (77.6)	90 (72.0)
Vaccinations received according to protocol — no. (%)		
Meningococcal	125 (100.0)	125 (100.0)
Pneumococcal	125 (100.0)	125 (100.0)
Type II diabetes — no. (%)		
Yes	5 (4.0)	10 (8.0)
No	120 (96.0)	115 (92.0)
Previous treatments for IgA nephropathy — no. (%)††		
Glucocorticoids	37 (29.6)	36 (28.8)
Other immunosuppressants	19 (15.2)	11 (8.8)
FACIT-Fatigue total score‡‡	42.1±8.2	42.8±7.9

* Plus–minus values are means ±SD. Data are shown for the interim analysis, which included the first 250 patients who had undergone randomization and completed the month 9 visit or discontinued the trial by month 9. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, eGFR estimated glomerular filtration rate, IQR interquartile range, and SGLT2 sodium–glucose cotransporter 2.

† The Asia category includes China, India, Japan, South Korea, Vietnam, Singapore, Taiwan, Malaysia, and Thailand.

‡ The Oxford Classification of IgA nephropathy MEST-C score is based on five indicators: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy or interstitial fibrosis (T), and the presence of crescents (C). For dual categories (M, E, and S), a score of 1 indicates evidence of respective lesions in biopsy specimens, and 0 the absence. For other categories (T and C), a higher score indicates a larger extent of the lesion. The M score was not available for 9 patients in the iptacopan group and 6 patients in the placebo group; the E score was not available for 10 patients and 8 patients, respectively; the S score was not available for 10 patients and 7 patients, respectively; the T score was not available for 9 patients and 5 patients, respectively; and the C score was not available for 14 patients and 18 patients, respectively. The MEST-C scores were determined by local pathologists on the basis of the qualifying biopsy and were reported by the investigator.

§ This category also includes ACE inhibitors or ARBs as part of a multidrug compound. The maximal dose is that according to the label of the respective compound in the respective region.

¶ The actual value is not shown in order to conceal individual patient data.

‖ Systolic and diastolic blood pressure data are summarized for 249 patients who had measurements taken while they were in a seated position.

** Hematuria was defined as a dipstick reading of more than 1+.

†† Patients who were receiving glucocorticoids (in doses of more than 7.5 mg per day of prednisone equivalent) or other immunosuppressive medications had to stop taking these agents within 90 days before starting the trial regimen.

‡‡ Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) total scores range from 0 to 52, with higher scores indicating less fatigue.

inine ratio, total 24-hour urinary protein excretion, and 24-hour albumin excretion were consistent with those of the primary analysis (Fig. S4).

The results of the supplementary intention-to-treat analysis of the 24-hour urinary protein-to-creatinine ratio were consistent with those of the primary analysis; the ratio was 37.9% (95% CI, 25.8 to 48.0) lower in the iptacopan group than in the placebo group (Table S3). The treatment effect with respect to the primary end point was consistent across subgroups defined according to sex, geographic region, baseline 24-hour urinary protein-to-creatinine ratio, baseline eGFR, baseline SGLT2 inhibitor use, baseline hematuria level, MEST-C score, and previous use of glucocorticoids or other immunosuppressants (Fig. 3 and Fig. S5). The percentage of patients who had a urinary protein-to-creatinine ratio of less than 1 at month 9 without receiving rescue or alternative medication or undergoing kidney-replace-

ment therapy was higher in the iptacopan group (42.5%; 95% CI, 34.5 to 50.5) than in the placebo group (21.9%; 95% CI, 14.8 to 29.0) (odds ratio, 3.12; 95% CI, 1.68 to 5.79) (Table S4). A similar trend was observed in the analysis of the proportion of patients who had a urinary protein-to-creatinine ratio of less than 0.5 at month 9 (Table S5).

BIOMARKERS, FACIT-FATIGUE SCORE, AND HEMATURIA LEVELS

The changes in complement pathway biomarkers were consistent with selective alternative pathway inhibition. In the iptacopan group, the urinary terminal membrane attack complex (sC5b-9), which had been markedly elevated at baseline, returned to a level that was within the range

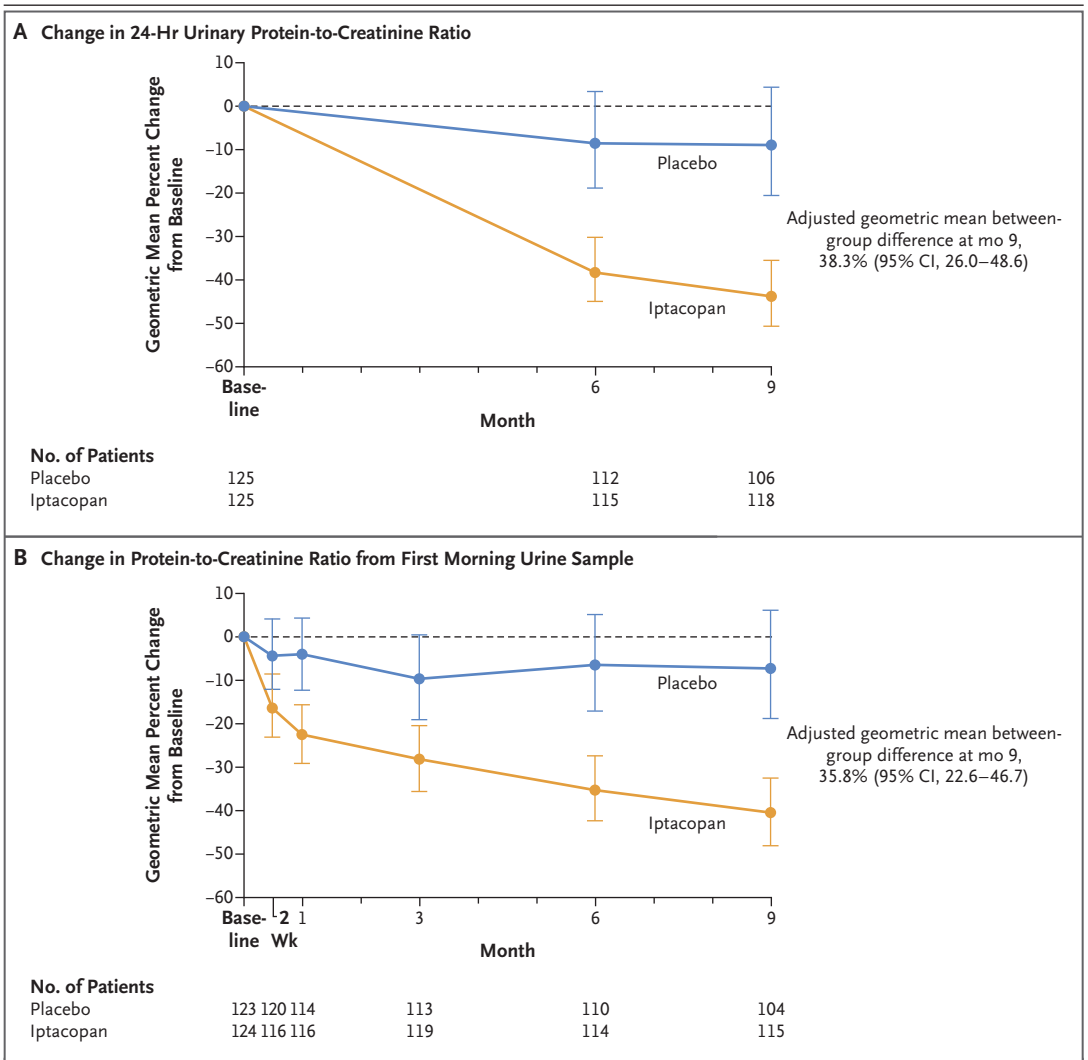

Figure 2. Changes in Urinary Protein-to-Creatinine Ratio.

Panel A shows the protein-to-creatinine ratio (with protein and creatinine both measured in grams) based on 24-hour urine sample collection over time in each trial group. Panel B shows the protein-to-creatinine ratio based on the first morning urine sample over time in each trial group. The I bars indicate 95% confidence intervals. The number at baseline represents the number of patients included in the analysis (i.e., patients with nonmissing baseline data and nonmissing covariates). The number at each visit is the number of patients with nonmissing values and values that were not imputed in accordance with the intercurrent event–handling strategy. The log-transformed ratios to baseline were analyzed with the use of a repeated measures model. The results were back-transformed and are presented as percentages. Data in Panel B are from Rizk et al.[32]; adapted with permission.

Subgroup	Iptacopan	Placebo	Iptacopan vs. Placebo, Percent Difference (95% CI)	P Value
	no. of patients/total no.			
Overall	118/125	106/125	38.3 (26.0 to 48.6)	<0.001
Sex				
Male	68/71	49/60	35.5 (17.4 to 49.7)	
Female	50/54	57/65	42.6 (24.5 to 56.4)	
Geographic region				
Asia	63/64	55/64	31.6 (13.4 to 46.0)	
All other regions	55/61	51/61	45.5 (28.3 to 58.5)	
24-Hr urinary protein-to-creatinine ratio at baseline				
<1.5	45/45	30/34	27.3 (2.4 to 45.9)	
≥1.5	73/80	76/91	41.2 (26.0 to 53.2)	
<2	71/71	59/67	35.0 (18.8 to 48.0)	
≥2	47/54	47/58	41.2 (20.9 to 56.4)	
eGFR at baseline				
30 to <45 ml/min/1.73 m^2	32/36	27/34	45.4 (25.3 to 60.1)	
≥45 ml/min/1.73 m^2	86/89	79/91	35.1 (19.0 to 48.0)	
SGLT2 inhibitor use at baseline				
Yes	16/18	12/14	36.7 (4.4 to 58.1)	
No	102/107	94/111	38.1 (24.4 to 49.2)	
Hematuria at baseline				
≥1	93/97	74/90	35.4 (21.8 to 46.7)	
Negative or trace	20/23	28/30	42.8 (6.1 to 65.2)	
M score				
M1	69/76	66/80	44.3 (28.7 to 56.5)	
M0	40/40	35/39	20.8 (–6.1 to 40.9)	
E score				
E1	32/36	30/36	39.2 (19.1 to 54.3)	
E0	76/79	69/81	37.4 (20.1 to 50.9)	
S score				
S1	81/87	81/89	35.3 (19.2 to 48.2)	
S0	27/28	19/29	39.4 (13.2 to 57.7)	
T score				
T1 or T2	46/48	44/53	34.4 (15.0 to 49.4)	
T0	63/68	58/67	40.3 (21.8 to 54.5)	
C score				
C1 or C2	32/35	17/22	45.5 (15.0 to 65.0)	
C0	72/76	72/85	32.5 (15.2 to 46.2)	

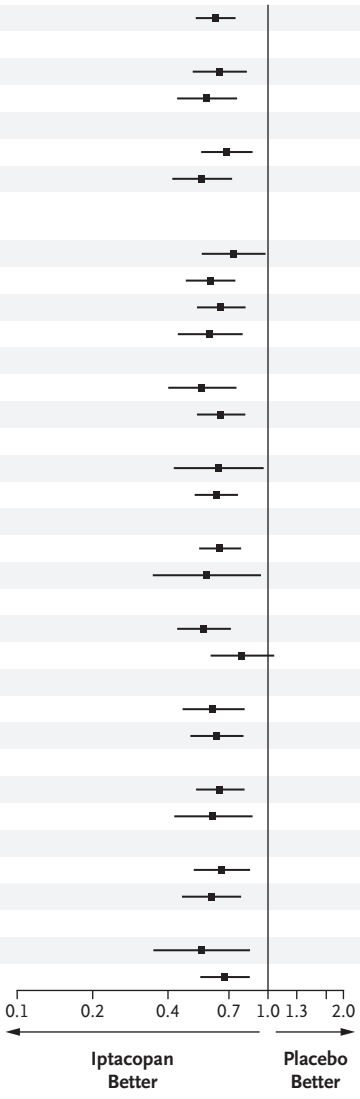

Figure 3. Subgroup Analyses.

Shown are subgroup analyses of the reduction in the 24-hour urinary protein-to-creatinine ratio (with protein and creatinine both measured in grams) from baseline to month 9. The number of patients represents those with nonmissing values and values that were not imputed in accordance with the intercurrent event–handling strategy at month 9. The total number of patients represents all the patients included in the analysis (patients with nonmissing baseline data and nonmissing covariates). The P value is two-sided. Geographic region, eGFR at baseline, and 24-hour urinary protein-to-creatinine ratio (<2 vs. ≥2) were stratification criteria at randomization. Hematuria at baseline was determined on the basis of dipstick testing. The Oxford Classification of IgA nephropathy MEST-C score is based on five indicators: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy or interstitial fibrosis (T), and the presence of crescents (C). For dual categories (M, E, and S), a score of 1 indicates evidence of respective lesions in biopsy specimens, and 0 the absence. For other categories (T and C), a higher score indicates a larger extent of the lesion. SGLT2 denotes sodium–glucose cotransporter 2.

Table 2. Adverse Events.*

Adverse Event	Iptacopan (N=222)	Placebo (N=221)
	no. of patients (%)	
Any adverse event†	138 (62.2)	153 (69.2)
Adverse events occurring in ≥5% of patients in either group†		
Covid-19	31 (14.0)	37 (16.7)
Upper respiratory tract infection	20 (9.0)	16 (7.2)
Nasopharyngitis	11 (5.0)	16 (7.2)
Headache	9 (4.1)	12 (5.4)
Hypertension	4 (1.8)	13 (5.9)
Serious adverse event†	18 (8.1)	11 (5.0)
Severe adverse event†	7 (3.2)	7 (3.2)
Adverse event leading to discontinuation of iptacopan or placebo	6 (2.7)	6 (2.7)
Death	0	0

* Safety was assessed in all the patients in the main trial population who had received at least one dose of iptacopan or placebo at the time of the data cutoff for the interim analysis. Patients with multiple occurrences of an adverse event are counted only once under that category. Adverse events were classified according to the preferred term of the *Medical Dictionary for Regulatory Activities*, version 26.0. Covid-19 denotes coronavirus disease 2019.

† Included are events that started during the treatment period, or events that were present before but increased in severity during the treatment period. The treatment period is defined as starting on the date of the first administration of iptacopan or placebo and ending 7 days after the date of the last administration of iptacopan or placebo in the core trial or ending on the date of first administration of iptacopan or placebo in the rollover extension program (whichever occurred first).

observed in healthy persons (Fig. S6). Among patients who had hematuria at baseline, hematuria was no longer present at month 9 in 38.7% (95% CI, 28.8 to 49.4) of the patients in the iptacopan group and in 16.3% (95% CI, 9.2 to 25.8) of those in the placebo group (Fig. S7). The changes from baseline in FACIT-Fatigue scores were similar in the two groups at month 9 (Table S6).

SAFETY

The incidence of adverse events after initiation of iptacopan or placebo was similar in the two groups, and most were mild to moderate in severity (Table 2). The most common adverse events (those that occurred in ≥5% of the patients in either group) were Covid-19 (coronavirus disease 2019), upper respiratory tract infection, nasopharyngitis, headache, and hypertension, with hypertension reported more frequently in the placebo group than in the iptacopan group (Table 2). No increased risk of infection was observed; 33.8% of the patients in the iptacopan group and 38.5% of those in the placebo group had infections and infestations (*Medical Dictionary for Regulatory Activities* system organ class). Infections with microbiologic confirmation of encapsulated bacteria occurred in less than 0.5% of the patients; all these patients recovered after treatment with antibiotic agents. Few patients (2.7% in each group) discontinued iptacopan or placebo because of adverse events. Diastolic and systolic blood pressures remained generally constant in both groups throughout the trial (Fig. S8). No deaths occurred.

DISCUSSION

While the presence of complement in the glomeruli of patients with IgA nephropathy on kidney biopsy has long been observed,[12-18] increasing evidence suggests that complement activity plays a role in glomerular inflammation and tubulointerstitial damage.[33,34] In this trial, treatment with iptacopan, an agent that acts through inhibition of the alternative complement pathway,[35] resulted in a significant reduction in proteinuria of 38.3% (95% CI, 26.0 to 48.6; P<0.001) relative to placebo, a finding that is likely to translate to important clinical benefits for kidney function,

on the basis of meta-analyses of previous randomized clinical trials.[36] The Food and Drug Administration (FDA) accepts proteinuria as a reasonably likely surrogate end point for delay in loss of kidney function, as measured with eGFR,[37] which supported the FDA's recent accelerated approval of iptacopan for the treatment of primary IgA nephropathy.[38]

The robust result of the primary analysis is supported by the consistency of results across secondary analyses. Proteinuria reduction was rapid, with effects seen as early as week 2, and a continued reduction was observed through month 9. Exploratory analyses (shown in the Supplementary Appendix) indicate that the effects on proteinuria that were observed align with biomarker-based mechanistic evidence of alternative complement pathway inhibition by iptacopan in IgA nephropathy — specifically, decreased concentrations of urinary complement terminal membrane attack complex that are within the range observed in healthy persons. The membrane attack complex elicits apoptosis and disruption of the glomerular filtration barrier, resulting in glomerular scarring owing to the release of proteases, cytokines, and extracellular matrix components.[18] Formation of the terminal membrane attack complex on tubular epithelial cells and exposure to C5a contribute to tubulointerstitial injury.[33,39]

The treatment effect of iptacopan on proteinuria was consistent across all subgroups, including patients from Asia and other regions outside Asia (Asian patients are traditionally considered to have a more inflammatory disease phenotype).[40] The current trial therefore provides support for the hypothesis that the alternative complement pathway plays an important role in kidney damage in IgA nephropathy. Given these results, we expect that iptacopan has a high likelihood of showing benefits for kidney function.

This trial is one of several that are currently assessing potential kidney- protective agents in IgA nephropathy. Recent trial data have led to approval of an oral, targeted-release budesonide formulation (Nefecon) for IgA nephropathy on the basis of a 27% (95% CI, 13 to 39) reduction in proteinuria at 9 months as compared with placebo,[24] and a decrease in the total eGFR slope of 2.95 ml per minute per 1.73 m^2 per year (95% CI, 1.67 to 4.58) over 2 years as compared with placebo.[41] Sparsentan, a combined endothelin–angiotensin receptor antagonist, received FDA approval for the treatment of IgA nephropathy after trial data showed a 41% (95% CI, 31 to 49) reduction in proteinuria at 9 months[42] and a decrease in total eGFR slope (1.0 ml per minute per 1.73 m^2 per year; 95% CI, −0.03 to 1.94) as compared with irbesartan.[43] Conversely, a trial of narsoplimab, an inhibitor of the lectin pathway of complement, was discontinued, as it did not significantly reduce proteinuria as compared with placebo.[44] Although direct comparisons of these agents cannot be made because of differences in trial designs and populations, the effects of iptacopan on proteinuria in our trial compare favorably with the results of those trials; the effects of iptacopan on eGFR slope await trial completion. Increasing evidence has led to suggestions of considering SGLT2 inhibitors for the treatment of IgA nephropathy on the basis of subgroup analyses in the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial and the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY).[45,46] Of note, patients in the iptacopan group who were receiving SGLT2 inhibitors at baseline in the current trial had similar reductions in proteinuria to those who were not taking those agents, which may indicate that combination therapy could offer additive benefits. The most appropriate approach to individual and combination therapies for IgA nephropathy will be an important area of future study.

There were no serious safety problems reported in this trial. No increases in infections were noted; however, all the patients were protected by vaccination at baseline against meningococcal and pneumococcal infections, as well as *H. influenzae* type B, if available and according to local regulations.[28]

The current trial is ongoing and will continue in a blinded fashion until completion, to assess the efficacy of iptacopan with respect to kidney function over 2 years (on the basis of the annualized rate of total eGFR slope) as well as safety. The strengths of this trial include the robust design and conduct, as well as the stringent requirement of maximum and stable doses of ACE inhibitors and ARBs, on the basis of baseline blood-pressure values. Enrolled patients had a relatively short time from the qualifying biopsy to trial entry as compared with participants in other studies in IgA nephropathy, a factor that

supports evaluation of treatment effect according to MEST-C categories. In addition, our trial included 50:50 recruitment in Asian versus non-Asian regions, as IgA nephropathy phenotypes historically are considered to differ between these populations.

This trial has certain limitations. The interim analysis was not designed to confirm the effects of iptacopan on eGFR or other measures of kidney function; these results have not yet been reported to avoid influencing the conduct of the ongoing trial, on the advice of regulatory agencies. Given its considerable effects on proteinuria, iptacopan may represent a targeted treatment for patients with IgA nephropathy by blocking complement-mediated injury. The ongoing trial should provide further evidence about the effects of iptacopan on kidney function, which will define the role of iptacopan in the management of IgA nephropathy.

In this interim analysis, treatment with iptacopan resulted in a significant reduction in proteinuria as compared with placebo.

Some of the data reported in the tables were previously presented at the International Society of Nephrology World Congress of Nephrology, Buenos Aires, April 13–16, 2024.

Supported by Novartis Pharma.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families; the investigators and staff at the participating trial sites; and Nupur Chaubey (Novartis India) and Helen Varley and Susan Simpson (Novartis Ireland) for medical writing and editorial support.

APPENDIX

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