ORIGINAL ARTICLE

Trial of Pegcetacoplan in C3 Glomerulopathy and Immune-Complex MPGN

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ABSTRACT

BACKGROUND

C3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis (MPGN) generally result in glomerular C3 deposition and irreversible kidney damage. The efficacy and safety of pegcetacoplan, a C3 and C3b inhibitor, in persons with C3 glomerulopathy or primary immune-complex MPGN are unclear.

METHODS

We conducted a phase 3, double-blind, placebo-controlled trial involving adolescents and adults with C3 glomerulopathy or primary immune-complex MPGN, including those with native kidney disease and those with disease recurrence after transplantation. Patients were randomly assigned in a 1:1 ratio to receive pegcetacoplan or placebo. The primary end point was the log-transformed ratio of the urinary protein-to-creatinine ratio at week 26 as compared with baseline.

RESULTS

A total of 124 patients underwent randomization. The change in proteinuria (as measured by the log-transformed ratio to baseline in the urinary protein-to-creatinine ratio) was significantly greater with pegcetacoplan than with placebo (geometric mean of the urinary protein-to-creatinine ratio, −67.2% [95% confidence interval {CI}, −74.9 to −57.2] vs. 2.9% [95% CI, −8.6 to 15.9]). The difference represents a relative reduction of 68.1% (95% CI, 57.3 to 76.2) as compared with placebo. In hierarchical testing of five secondary end points, significantly higher percentages of patients in the pegcetacoplan group than in the placebo group met the composite renal end-point criteria (stabilization of estimated glomerular filtration rate [eGFR] and ≥50% reduction in urinary protein-to-creatinine ratio) (49% vs. 3%) and had at least a 50% reduction in the protein-to-creatinine ratio (60% vs. 5%). Among 69 patients with evaluable kidney-biopsy samples, the change in the activity score of the C3 glomerulopathy histologic index did not differ significantly between the two groups; subsequent end points (decrease in C3 staining and change in eGFR) were not formally tested. Pegcetacoplan was not associated with more adverse events than placebo. No serious infections from encapsulated bacteria occurred; 1 patient receiving pegcetacoplan died from coronavirus disease 2019 pneumonia. No allograft rejection or loss occurred.

CONCLUSIONS

Pegcetacoplan resulted in a significantly greater reduction in proteinuria than placebo among patients with C3 glomerulopathy or primary immune-complex MPGN. (Funded by Apellis Pharmaceuticals and Sobi [Swedish Orphan Biovitrum]; VALIANT ClinicalTrials.gov number, NCT05067127.)

C3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis (MPGN) are rare glomerulopathies characterized by C3 dysregulation that generally lead to abnormal glomerular C3 deposition and irreversible kidney damage.[1-3] Within 10 years after diagnosis, up to 50% of patients have progression to advanced kidney failure that leads to dialysis or transplantation.[4,5] Recurrent C3 glomerulopathy leads to allograft loss in up to 60% of grafts.[6,7] Although primary immune-complex MPGN has a distinct histology characterized by immunoglobulin deposition in addition to the glomerular C3 deposition observed in C3 glomerulopathy,[8] complement dysregulation is central to the pathogenesis of both.[3]

Pegcetacoplan binds C3 and its activation fragment C3b, thereby regulating C3 cleavage and generation of downstream complement effectors.[9] By targeting C3 and C3b, pegcetacoplan inhibits complement activation through the classical, lectin, and alternative complement pathways. Furthermore, pegcetacoplan directly inhibits C3 and C5 convertases by inhibiting C3b in both complexes.[9] Consequently, pegcetacoplan is predicted to halt glomerular C3 and C5 activation in C3 glomerulopathy and primary immune-complex MPGN, which could prevent glomerular complement deposition and kidney failure.[10]

In two phase 2 trials, pegcetacoplan showed efficacy and safety in patients with C3 glomerulopathy or primary immune-complex MPGN, including those with native kidney disease and those with disease recurrence after transplantation.[10,11] Here, we report the primary analysis of the VALIANT trial, which evaluated the efficacy and safety of pegcetacoplan as compared with placebo in adolescents and adults with recurrent C3 glomerulopathy or primary immune-complex MPGN, including those with native kidney disease and those with disease recurrence after transplantation.

Methods

Trial Design and Oversight

This phase 3, double-blind, randomized, placebo-controlled trial was conducted at 122 centers in 19 countries (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial included a 10-week screening period; a 26-week randomized, controlled period; a 26-week open-label period; and an 8-week follow-up period for patients who did not enroll in the long-term extension (VALE; ClinicalTrials.gov number, NCT05809531) (Fig. S1). Eligible patients were randomly assigned in a 1:1 ratio (with the use of a computer-generated randomization schedule) to receive pegcetacoplan or placebo. Randomization was stratified according to transplantation status and baseline biopsy availability. At the end of the randomized, controlled period, kidney biopsy was required for all the adults (see the Methods section in the Supplementary Appendix). The trial protocol is available at NEJM.org.

A Quick Take is available at NEJM.org

One of the sponsors (Apellis Pharmaceuticals) designed the trial, which was conducted in accordance with the International Council for Harmonisation E6 guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, all applicable regulatory requirements, and the requirements of the institutional review board or independent ethics committee at each site. Data were collected by trial investigators, reviewed by an independent data monitoring committee, analyzed by Apellis Pharmaceuticals, and available to all the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Confidentiality agreements were in place between authors and the sponsor. Patients provided written informed consent (and assent if applicable) before participation. The sponsors (Apellis Pharmaceuticals and Sobi [Swedish Orphan Biovitrum]) made the decision to submit the manuscript for publication. Kay Square Scientific provided writing assistance, funded by the sponsors. All the authors reviewed and approved the manuscript before submission.

Patients

Eligible patients were adolescents (12 to 17 years of age) or adults (≥18 years of age) with a diagnosis of primary C3 glomerulopathy or primary immune-complex MPGN (established on the basis of a baseline kidney biopsy ≤28 weeks before randomization or a historical kidney biopsy >28 weeks before randomization [adolescents only]) and evidence of active disease. In adolescents with a baseline biopsy and all the adults, active disease was defined as a score of 2+ or higher on C3 immunofluorescence staining (on a 0 to 3 scale, with higher scores indicating more intense C3 deposition) in the baseline biopsy reviewed by the

central pathologist.[12] In adolescents without a baseline biopsy, active disease was defined as at least one of the following: a plasma concentration of soluble C5b-9 of more than 207 ng per milliliter (upper limit of the normal range), a serum concentration of C3 of less than 90 mg per deciliter (lower limit of the normal range), the presence of active urine sediment, or the presence of C3 nephritic factor (see the Methods section in the Supplementary Appendix for details and additional entry criteria). Patients with a history of kidney transplantation were included.

Patients were required to be receiving stable (for ≥12 weeks before randomization) and appropriate (per investigator's discretion) supportive care regimens, which included angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, or sodium–glucose cotransporter 2 inhibitors, and could include immunosuppressive medications (e.g., mycophenolate mofetil or low-dose systemic glucocorticoids [prednisone dose of ≤20 mg per day or equivalent]). Patients who entered the trial while receiving immunosuppressive medications continued such treatment at stable doses. Appropriate supportive care was shown by consistent blood-pressure control (Fig. S2). Anticipated dose adjustments of immunosuppressive agents and other transplant-related medications (documented before randomization) were allowed for patients who had received a transplant. Vaccinations were required (see the Methods section in the Supplementary Appendix).

All the adults as well as adolescents weighing at least 50 kg received 1080 mg of pegcetacoplan or placebo by subcutaneous injection (administered by the patient or a trained caregiver) twice weekly in addition to appropriate supportive care. Adolescents weighing less than 50 kg received weight-adjusted doses. Rescue treatments were permitted. See the Methods section in the Supplementary Appendix for details about dose administration and rescue treatments.

END POINTS AND ASSESSMENTS

The primary efficacy end point was the log-transformed ratio of the urinary protein-to-creatinine ratio (from triplicate first-morning spot urine samples) at week 26 as compared with baseline, calculated with the use of an equal-weighted average over weeks 24, 25, and 26. The primary efficacy end point was further analyzed according to prespecified subgroups. Key secondary efficacy end points that were evaluated at week 26 were tested hierarchically: a composite renal end point (stabilization of estimated glomerular filtration rate [eGFR; ≤15% reduction] and ≥50% reduction in urinary protein-to-creatinine ratio), at least a 50% reduction in the urinary protein-to-creatinine ratio, the change in the activity score of the C3 glomerulopathy histologic index[4] in patients with evaluable kidney-biopsy samples, a decrease in C3 staining by at least two orders of magnitude in immunofluorescence intensity in patients with evaluable kidney-biopsy samples, and the change in the eGFR (see the Methods section in the Supplementary Appendix for details). Adherence assessments are described in the Supplementary Appendix.

Safety was evaluated throughout the trial. Adverse events were documented according to the *Medical Dictionary for Regulatory Activities*, version 26.0.

STATISTICAL ANALYSIS

The primary analysis (all efficacy and safety end points at 26 weeks) was conducted when all the patients completed the week 26 assessment or discontinued the trial. Efficacy end points were analyzed in the intention-to-treat population, which included all the patients who underwent randomization. The safety population included all the patients who received at least one dose of pegcetacoplan or placebo. Longitudinal assessments for changes from baseline in continuous end points were analyzed with the use of a mixed-effects model for repeated measures. Binary end points were analyzed with the use of a logistic-regression model to determine the P values and odds ratios. Although odds ratios were evaluated and calculated in accordance with the statistical analysis plan, we present relative risks instead because this facilitates interpretation of the magnitude of effect. The key secondary end point of the activity score of the C3 glomerulopathy histologic index was analyzed with the use of an analysis-of-covariance model. See the Methods section of the Supplementary Appendix for the handling of missing data and intercurrent events and for sample-size justification.

A fixed-sequence hierarchical testing strategy was used for testing the key secondary end points while controlling the overall type I error. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in

place of hypothesis testing. The data-cutoff date for this primary analysis was June 20, 2024.

RESULTS

PATIENTS

Between May 30, 2022, and June 20, 2024, a total of 261 patients were screened, and 124 were randomly assigned to receive pegcetacoplan (63 patients) or placebo (61 patients) and were included in the intention-to-treat and safety populations (Fig. S3). A total of 6 of 124 patients discontinued the trial regimen: 2 in the pegcetacoplan group (owing to adverse events) and 4 in the placebo group (owing to an adverse event, withdrawal of consent, pregnancy, and patient nonadherence [1 patient each]). At the data-cutoff date, 2 patients (both in the pegcetacoplan group) had completed week 26 assessments but had not started the open-label period; they were classified as receiving ongoing treatment. In all, 59 patients (94%) in the pegcetacoplan group and 57 patients (93%) in the placebo group completed the 26-week randomized, controlled period and continued into the open-label period. All the patients in the safety population received at least 80% of the assigned doses of pegcetacoplan or placebo. Two patients (both in the placebo group) received glucocorticoid rescue treatment (see the Results section in the Supplementary Appendix). Eight patients (2 in the pegcetacoplan group and 6 in the placebo group) had intercurrent events (Table S2).

The characteristics of the patients at baseline were generally similar in the two trial groups, although patients who received pegcetacoplan were older and had a higher urinary protein-to-creatinine ratio and a lower eGFR than those who received placebo (Table 1 and Table S3). Overall, 96 of 124 patients (77%) had C3 glomerulopathy. A total of 9 of 124 patients (7%) had received a kidney transplant; one such patient was an adolescent. Demographic characteristics aligned with those previously reported, which suggests that the trial population is representative and that the findings can be generalized (Table S4).[13] Immunosuppressive treatment was ongoing in 89 of 124 patients (72%). Adolescents (mean age, 14.7 years; 50 with historical biopsies) comprised 55 of 124 patients (44%). Patients according to subgroups are shown in the Results section in the Supplementary Appendix.

CLINICAL EFFICACY

Primary End Point

Pegcetacoplan treatment for 26 weeks resulted in a significantly greater reduction in proteinuria, as measured by the log-transformed ratio to baseline in the urinary protein-to-creatinine ratio, than placebo (geometric mean of the urinary protein-to-creatinine ratio, −67.2% [95% confidence interval {CI}, −74.9 to −57.2] vs. 2.9% [95% CI, −8.6 to 15.9]). The difference represents a relative reduction with pegcetacoplan of 68.1% (95% CI, 57.3 to 76.2; P<0.001) (Fig. 1A). The proteinuria reduction with pegcetacoplan was observed as early as week 4 (at the time of the first sample collection after treatment initiation) and sustained through week 26; proteinuria was largely unchanged with placebo (Figs. S4 and S5). The reduction in proteinuria was broadly consistent across patient subgroups, including immunosuppressant status (Fig. 1B and Table S5).

Secondary End Points

Significantly more patients who received pegcetacoplan met the composite renal end-point criteria at week 26 than those who received placebo (49% [31 of 63 patients] vs. 3% [2 of 61 patients]; relative risk, 14.4 [95% CI, 3.7 to 56.9]; P<0.001) (Table 2, Fig. S6, and Table S6). This difference was mainly driven by a reduction in proteinuria, with 38 of 63 patients (60%) in the pegcetacoplan group having at least a 50% reduction in the urinary protein-to-creatinine ratio, as compared with 3 of 61 patients (5%) in the placebo group (relative risk, 12.0 [95% CI, 4.0 to 36.1]; P<0.001) (Table 2 and Fig. S7). In a post hoc analysis, the proteinuria reduction with pegcetacoplan corresponded to a substantial increase in the percentage of patients with a urinary protein-to-creatinine ratio of less than 1 (with both protein and creatinine measured in grams) at week 26 (8% at baseline vs. 51% at week 26) and a marked decrease in the percentage with a value in the nephrotic range of 3 or more (38% vs. 14%) (Fig. S8). More patients in the pegcetacoplan group than in the placebo group had a stable or improved eGFR (≤15% reduction) (43 of 63 [68%] vs. 36 of 61 [59%]).

Although the change in the activity score of the C3 glomerulopathy histologic index was numerically greater with pegcetacoplan than with placebo, the between-group difference was not significant at week 26 (Table 2 and Fig. S9). Con-

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

Characteristic	Pegcetacoplan (N=63)	Placebo (N=61)	Overall (N=124)
Age group — no. (%)			
Adolescents: 12–17 yr	28 (44)	27 (44)	55 (44)
Adults: ≥18 yr	35 (56)	34 (56)	69 (56)
Mean age — yr			
Among adolescents	14.6±1.7	14.8±1.8	14.7±1.7
Among adults	39.1±15.9	30.6±15.9	35.0±16.4
Female sex — no. (%)	37 (59)	33 (54)	70 (56)
Race or ethnic group — no. (%)†			
White	45 (71)	46 (75)	91 (73)
Asian	9 (14)	9 (15)	18 (15)
American Indian or Alaskan Native	1 (2)	0	1 (1)
Black or African American	1 (2)	0	1 (1)
Other	7 (11)	6 (10)	13 (10)
Underlying disease on basis of screening biopsy — no. (%)			
C3 glomerulopathy	51 (81)	45 (74)	96 (77)
Primary immune-complex MPGN	12 (19)	16 (26)	28 (23)
History of kidney transplantation — no. (%)	5 (8)	4 (7)	9 (7)
Median urinary protein-to-creatinine ratio (range)‡	2389.2 (713.6–11,418.0)	1815.6 (783.4–10,439.0)	2031.3 (713.6–11,418.0)
Median eGFR (range) — ml/min/1.73 m^2	78 (25–161)	91 (24–156)	86 (24–161)
Concomitant therapies — no. (%)§			
Renin–angiotensin system blocking agent	57 (90)	56 (92)	113 (91)
Immunosuppressant	47 (75)	42 (69)	89 (72)
Systemic glucocorticoid	25 (40)	24 (39)	49 (40)
Sodium–glucose cotransporter 2 inhibitor¶	7 (11)	6 (10)	13 (10)

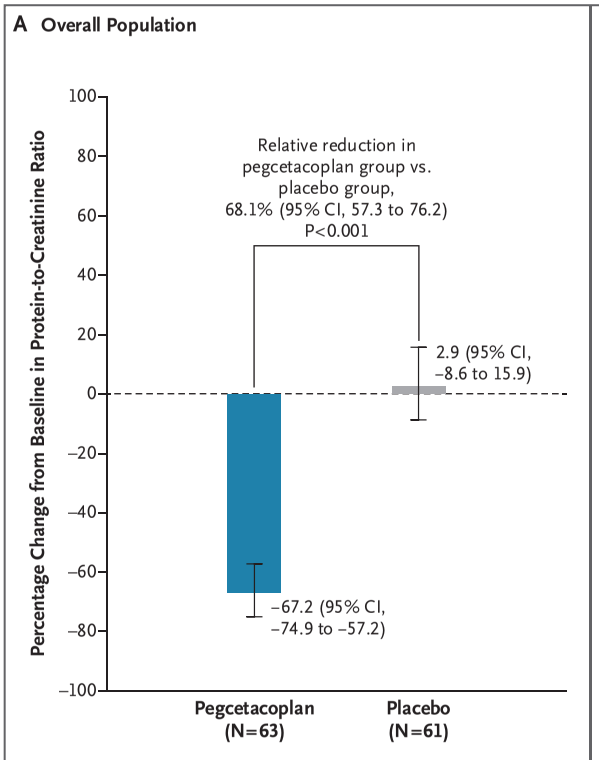
* Plus–minus values are means ±SD. This table includes patients in the intention-to-treat population (defined as all the patients who underwent randomization), unless otherwise specified. The term eGFR denotes estimated glomerular filtration rate, and MPGN membranoproliferative glomerulonephritis.
† Race or ethnic group was reported by the patient among a prespecified list of options.
‡ The ratio was determined from triplicate first-morning spot urine samples. Protein was measured in milligrams, and creatinine was measured in grams.
§ Concomitant therapies are shown for patients in the safety population, defined as all the patients who received at least one dose of pegcetacoplan or placebo.
¶ Drugs included in this category are dapagliflozin, dapagliflozin propanediol monohydrate, and empagliflozin.

sequently, subsequent end points were not tested for signficance.

A decrease in C3 staining at week 26 was observed in 26 of 35 patients (74%) with pegcetacoplan and in 4 of 34 patients (12%) with placebo (relative risk, 6.2; 95% CI, 2.4 to 15.9) (Table 2). Staining decreased to 0 intensity in 25 of 35 patients (71%) receiving pegcetacoplan and in 3 of 34 patients (9%) receiving placebo (Fig. 2).

From baseline to week 26, the least-squares mean change in the eGFR was –1.5 ml per minute per 1.73 m^2 (95% CI, –5.9 to 2.9) with pegcetacoplan and –7.8 ml per minute per 1.73 m^2 (95% CI, –11.6 to –4.0) with placebo (least-squares mean difference, 6.3 ml per minute per 1.73 m^2; 95% CI, 0.5 to 12.1) (Table 2 and Fig. S10). See Table S7 for data on additional secondary end points.

Serum C3 levels appeared to be higher and plasma levels of soluble C5b-9 appeared to be



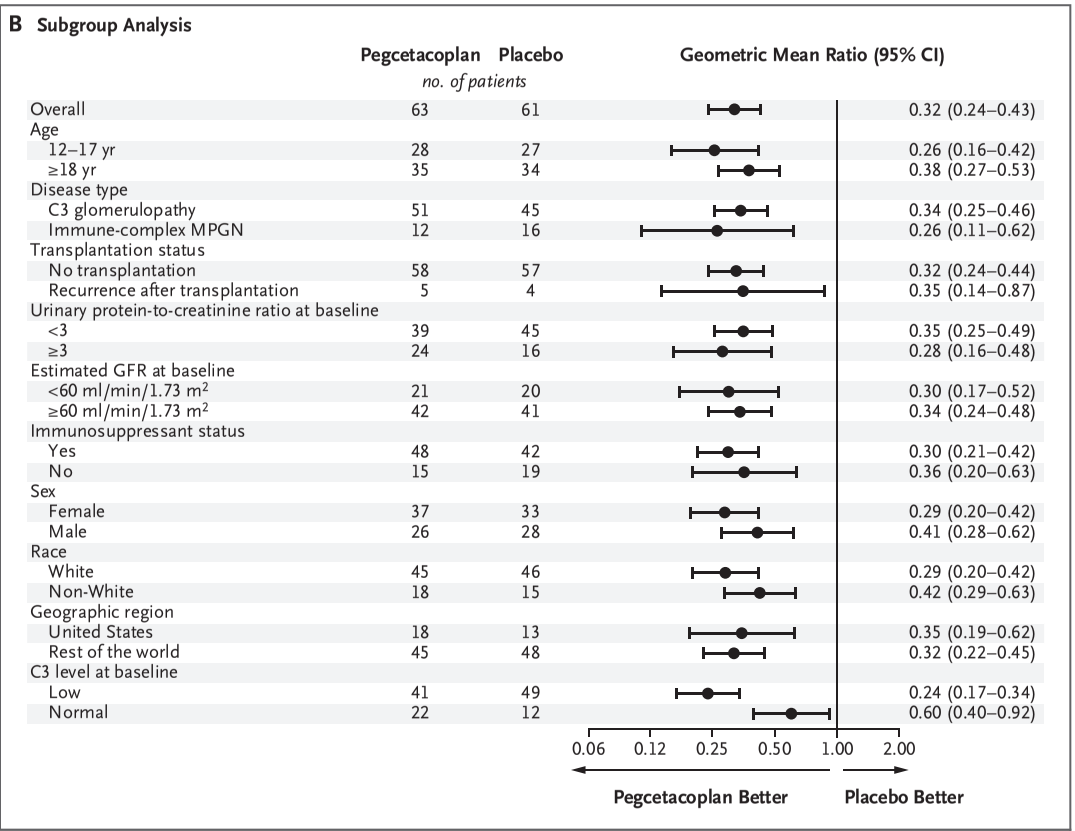


Figure 1. Change in Urinary Protein-to-Creatinine Ratio at Week 26.

Panel A shows the geometric mean of change from baseline at week 26 in the urinary protein-to-creatinine ratio (overall population), and Panel B shows the geometric mean ratio of the change in the pegcetacoplan group as compared with the change in the placebo group (subgroup analysis). This analysis was performed with the use of a mixed-effects model for repeated measures in the intention-to-treat population (all the patients who underwent randomization). The urinary protein-to-creatinine ratio at baseline (with both protein and creatinine measured in grams) was calculated as the equal-weighted average of the measurements from at least six of the nine first-morning spot urine samples collected between the start of screening and day 1, inclusive. The widths of the 95% confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Immunosuppressant status was based on "immunosuppressants," "corticosteroids for systemic use," or both according to Anatomical Therapeutic Chemical level 2 codes. GFR denotes glomerular filtration rate, and MPGN membranoproliferative glomerulonephritis.

Table 2. Key Secondary End Points.*

End Point	Pegcetacoplan	Placebo	Pegcetacoplan vs. Placebo		P Value
			Measure	Value (95% CI)	
Composite renal end point: stabilization of eGFR and ≥50% reduction in UPCR at wk 26†					
No. of patients evaluated	63	61			
Patients with response — no. (%)	31 (49)	2 (3)	Relative risk‡	14.4 (3.7 to 56.9)	<0.001§
≥50% Reduction in UPCR at wk 26					
No. of patients evaluated	63	61			
Patients with response — no. (%)	38 (60)	3 (5)	Relative risk‡	12.0 (4.0 to 36.1)	<0.001§
Change in activity score of C3 glomerulopathy histologic index from baseline at wk 26¶‖					
No. of patients evaluated	35	34			
LSM change (95% CI)	−3.5 (−4.7 to −2.2)	−2.5 (−3.8 to −1.2)	Adjusted mean difference	−1.0 (−2.8 to 0.8)	0.28
Decrease in C3 staining of ≥2 orders of magnitude at wk 26‖					
No. of patients evaluated	35	34			
Patients with response — no. (%)	26 (74)	4 (12)	Relative risk‡	6.2 (2.4 to 15.9)	
Change in eGFR from baseline at wk 26					
No. of patients evaluated	63	61			
LSM change (95% CI) — ml/min/1.73 m^2	−1.5 (−5.9 to 2.9)	−7.8 (−11.6 to −4.0)	LSM difference	6.3 (0.5 to 12.1)	

* A fixed-sequence testing strategy was used. Statistical significance of the first secondary end point was evaluated only if statistical significance was achieved with the prespecified primary analysis of the primary end point. A fixed-sequence hierarchical testing strategy was used for testing the key secondary end points while controlling the overall type I error. Although odds ratios were evaluated and calculated in accordance with the statistical analysis plan, we present relative risks instead because this facilitates interpretation of the magnitude of effect. LSM denotes least-squares mean, and UPCR urinary protein-to-creatinine ratio.

† Stabilization of the eGFR was defined as a reduction of no more than 15%.

‡ Covariate-adjusted relative risks and corresponding 95% confidence intervals are reported for binary end points with the use of a modified Poisson regression model as a post hoc analysis.

§ The P value is based on logistic regression or hypothesis testing for the odds ratios (shown in Table S6).

¶ The C3 glomerulopathy histologic index activity score measures disease activity on a semiquantitative scale of 0 to 3 to assess seven markers of C3 glomerulopathy activity. Activity scores range from 0 (lowest activity) to 21 (highest activity).[4]

‖ Kidney-biopsy end points were evaluated only for adult patients.

lower after pegcetacoplan treatment, as compared with baseline values. C4 levels appeared to be similar before and after treatment (Fig. S11).

SAFETY

The incidence of adverse events during the treatment period was similar in the pegcetacoplan and placebo groups (84% [53 of 63 patients] and 93% [57 of 61 patients], respectively), as was the incidence of adverse events that were considered by the investigator to be related to the trial regimen (40% [25 of 63 patients] and 43% [26 of 61 patients]) (Table 3). Serious adverse events occurred in 6 patients per group (10% in each group). Infections accounted for the serious adverse events in 3 patients (5%) who received pegcetacoplan (coronavirus disease 2019 [Covid-19] pneumonia, influenza, and pneumonia in 1 patient [2%] each) and in 1 patient (2%) who received placebo (viral infection). There was one death; a patient in the pegcetacoplan group died from respiratory failure associated with Covid-19 pneumonia (see the Results section in the Supplementary Appendix). No serious infections caused by encapsulated bacteria were reported. There were no cases of allograft rejection or loss.

DISCUSSION

Targeted therapies are needed for complement-mediated kidney diseases. Patients with C3 glomerulopathy or primary immune-complex MPGN

A Shifts in C3 Staining in Adult Patients

		C3 Staining Intensity			
	Week 26	Baseline			
		0	≥1	≥2	≥3
		no. (%)			
Pegcetacoplan (N=35)	0	0	0	7 (20)	18 (51)
	≥1	0	0	1 (3)	1 (3)
	≥2	0	0	0	1 (3)
	≥3	0	0	0	5 (14)
	Missing	0	0	0	2 (6)
Placebo (N=34)	0	0	0	1 (3)	2 (6)
	≥1	0	0	0	1 (3)
	≥2	0	0	3 (9)	4 (12)
	≥3	0	0	1 (3)	17 (50)
	Missing	0	0	0	5 (15)

B Microscopy of Renal-Biopsy Samples from a Representative Patient after Pegcetacoplan Treatment

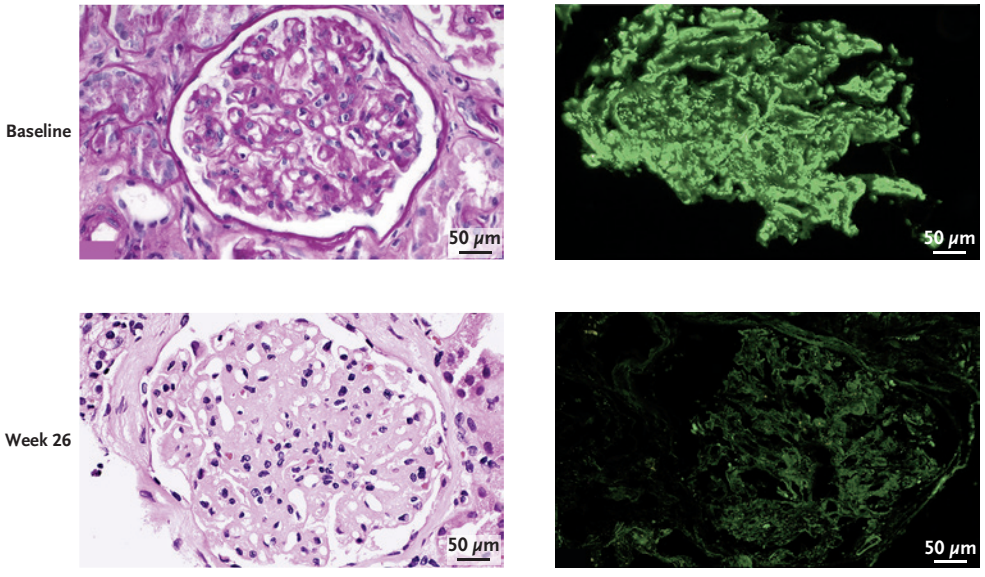


Figure 2. C3 Staining in Kidney Biopsies.

Panel A shows shifts in C3 staining in adult patients with evaluable kidney-biopsy samples in the intention-to-treat population, and Panel B shows light microscopic images of renal-biopsy samples from a patient with C3 glomerulopathy and a native kidney who had a C3 staining shift from +3 to 0 after 26 weeks of pegcetacoplan treatment. The image on the upper left shows mild mesangial expansion (periodic acid–Schiff stain), and the image on the upper right shows diffuse capillary loop and mesangial staining (fluorescein-conjugated antihuman C3 immunostain). The image on the lower left shows mesangial expansion (hematoxylin and eosin stain), and the image on the lower right shows essentially negative staining (fluorescein-conjugated antihuman C3 immunostain). Immunofluorescence staining is performed with antibodies against C3. This antibody does not interfere with the activity of pegcetacoplan.

who received pegcetacoplan in the present trial had a 68.1% relative reduction in proteinuria (vs. placebo). Although the hierarchical testing plan precluded formal hypothesis testing and no conclusions can be drawn, the results were consistent with a decrease in C3 staining (to 0 intensity in 71% of patients) and stabilization of the eGFR. This outcome triad aligns with the consensus recommendations for assessing the efficacy of treatment for C3 glomerulopathy.[12]

Table 3. Adverse Events.*

Adverse Event	Pegcetacoplan (N=63)	Placebo (N=61)
	number (percent)	
Any adverse event	53 (84)	57 (93)
Related to trial regimen†	25 (40)	26 (43)
Severe adverse event	3 (5)	4 (7)
Serious adverse event‡	6 (10)	6 (10)
Covid-19 pneumonia	1 (2)	0
Influenza	1 (2)	0
Pneumonia	1 (2)	0
Viral infection	0	1 (2)
Acute renal injury	1 (2)	2 (3)
Nephrotic syndrome	1 (2)	0
Proteinuria	0	1 (2)
Tubulointerstitial nephritis	0	1 (2)
Pyrexia	1 (2)	0
Respiratory failure	1 (2)	0
Hypertension	1 (2)	0
Vomiting	0	1 (2)
Blood creatinine increased	0	1 (2)
Spontaneous abortion	0	1 (2)
Pregnancy	0	1 (2)§
Adverse event leading to discontinuation from trial	1 (2)	1 (2)
Death	1 (2)¶	0

* Data are shown for patients in the safety population, which included all the patients who received at least one dose of pegcetacoplan or placebo. Shown are adverse events that emerged or worsened from the first dose up to 56 days after the last dose. Covid-19 denotes coronavirus disease 2019.
† The relatedness of the adverse event to the trial regimen was determined by the investigator.
‡ If a patient had multiple occurrences of an adverse event, the patient is counted only once in the patient count, whereas all occurrences contribute to the total event count.
§ Although pregnancy is considered to be a natural medical event, it is noted as an adverse event because it led to the patient's discontinuation from the trial.
¶ The death was due to Covid-19 pneumonia.

A reduction in proteinuria has disease-specific relevance for prognosis and treatment.[2] In other research, a 50% reduction correlated with a decreased risk of kidney failure (eGFR, <15 ml per minute per 1.73 m^2),[14] and the risk of kidney failure was 85% lower 12 months after diagnosis among patients who had reached a urinary protein-to-creatinine ratio (with protein measured in milligrams and creatinine measured in millimoles) of less than 300 than among those who had a ratio of more than 300.[13] Substantial proportions of the patients in our trial had similar proteinuria outcomes. In addition, abnormal glomerular C3 deposition is the pathogenic driver of kidney failure in C3 glomerulopathy, and restoration of C3 regulation ameliorates C3 glomerulopathy.[15,16] An early and rapid decline in the eGFR is associated with a higher likelihood of kidney failure,[13,17] which suggests that stabilization of the eGFR with pegcetacoplan may lead to better prognosis; validation of this concept would require further studies.

Pegcetacoplan showed efficacy in a broad population, including both adolescents and persons receiving immunosuppressive agents. An incidence of histologic recurrence of up to 89% has been reported[18,19]; the likelihood of recurrence is particularly high among adolescents, whose lifelong disease may result in the need for multiple transplants.[20] Efficacy in the post-transplantation context is supported by this trial and by the phase 2 NOBLE trial: 50% of patients had decreased C3 staining after 12 weeks of pegcetacoplan, and patients with a urinary protein-to-creatinine ratio (with both protein and creatinine measured in grams) of 1 or more at baseline had a median reduction in proteinuria of 54%.[11]

Because increased activation of complement causes C3 glomerulopathy and primary immune-complex MPGN, treatment with targeted complement inhibition is logical. Terminal complement inhibition with the C5 inhibitor eculizumab showed limited clinical benefit in patients with C3 glomerulopathy or primary immune-complex MPGN, probably owing to ongoing C3 activation.[21-26] Similarly, the C5a inhibitor avacopan did not show conclusive clinical benefit for C3 glomerulopathy.[27] Danicopan, a factor D inhibitor, did not show a benefit with respect to the key efficacy end points and did not result in sustained complement inhibition.[28] Iptacopan, a factor B inhibitor approved to reduce proteinuria in adults with C3 glomerulopathy,[29] led to reductions in the urinary protein-to-creatinine ratio of 35% at month 6 and 37% at month 12.[30,31] C3 staining was reduced by 0.8 points (on a 12-point scale, with higher values indicating greater C3 deposition) at month 6 with iptacopan; changes in the eGFR were not significant.[29-31]

Pegcetacoplan is a targeted C3 and C3b inhibitor that directly blocks both C3 and C5 activation through the classical, lectin, and alternative complement pathways, which inhibits downstream

effectors.[9,32] Although we did not perform formal testing, our findings with respect to complement activation and glomerular C3 staining provide support for the hypothesis that the significant benefit of pegcetacoplan with respect to the primary end point is due to its stopping the pathophysiological drivers of disease. Pegcetacoplan directly affects the complement activation underlying C3 glomerulopathy and primary immune-complex MPGN by inhibiting C3 and C3b, thereby reducing proteinuria independent of hemodynamic or antihypertensive treatments. Thus, pegcetacoplan may have an outcome distinct from approaches that reduce proteinuria without addressing complement dysregulation; such approaches may lead to insufficient proteinuria control and potential kidney failure.[33]

Pegcetacoplan had adverse events that were similar to those previously reported[11,34,35]; no infections by encapsulated meningococci were reported, a finding consistent with those of previous trials.[32] No allograft loss or rejection was reported during the trial.

Our trial has certain limitations; one limitation is the lack of long-term data on the efficacy and safety of pegcetcoplan in patients with C3 glomerulopathy or primary immune-complex MPGN. Such data are anticipated from the open-label period of this trial and the VALE extension. Furthermore, the activity score of the C3 glomerulopathy histologic index has not been validated as a predictor for the progression of C3 glomerulopathy.[36] In addition, few patients with a history of transplantation received pegcetacoplan. Finally, adolescent patients lacked follow-up biopsies, and only baseline information was collected on the etiologic factors of C3 glomerulopathy.

In this trial, pegcetacoplan resulted in a significantly greater reduction in proteinuria than placebo among patients with C3 glomerulopathy or primary immune-complex MPGN.

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REFERENCES

1. Pickering MC, D'Agati VD, Nester CM, et al. C3 glomerulopathy: consensus report. Kidney Int 2013;84:1079-89.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int 2021;100:S1-S276.
3. Vivarelli M, Barratt J, Beck LH Jr, et al. The role of complement in kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Kidney Int 2024;106:369-91.
4. Bomback AS, Santoriello D, Avasare RS, et al. C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy. Kidney Int 2018;93:977-85.
5. Servais A, Noël L-H, Roumenina LT, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int 2012;82:454-64.
6. Zand L, Lorenz EC, Cosio FG, et al. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. J Am Soc Nephrol 2014;25:1110-7.
7. Medjeral-Thomas NR, O'Shaughnessy

MM, O'Regan JA, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. Clin J Am Soc Nephrol 2014;9:46-53.
8. Fakhouri F, Le Quintrec M, Frémeaux-Bacchi V. Practical management of C3 glomerulopathy and Ig-mediated MPGN: facts and uncertainties. Kidney Int 2020; 98:1135-48.
9. Zwarthoff SA, Berends ETM, Mol S, et al. Functional characterization of alternative and classical pathway C3/C5 convertase activity and inhibition using purified models. Front Immunol 2018;9:1691.
10. Dixon BP, Greenbaum LA, Huang L, et al. Clinical safety and efficacy of pegcetacoplan in a phase 2 study of patients with C3 glomerulopathy and other complement-mediated glomerular diseases. Kidney Int Rep 2023;8:2284-93.
11. Bomback AS, Daina E, Remuzzi G, et al. Efficacy and safety of pegcetacoplan in kidney transplant recipients with recurrent complement 3 glomerulopathy or primary immune complex membranoproliferative glomerulonephritis. Kidney Int Rep 2024; 10:87-98.
12. Nester C, Decker DA, Meier M, et al. Developing therapies for C3 glomerulopathy: report of the Kidney Health Initiative C3 Glomerulopathy Trial Endpoints Work Group. Clin J Am Soc Nephrol 2024;19: 1201-8.
13. Masoud S, Wong K, Pitcher D, et al. Quantifying association of early proteinuria and estimated glomerular filtration rate changes with long-term kidney failure hazard in C3 glomerulopathy and immune-complex membranoproliferative glomerulonephritis using the United Kingdom RaDaR Registry. Kidney Int 2025;108:455-69.
14. Caravaca-Fontán F, Díaz-Encarnación M, Cabello V, et al. Longitudinal change in proteinuria and kidney outcomes in C3 glomerulopathy. Nephrol Dial Transplant 2022;37:1270-80.
15. Fakhouri F, de Jorge EG, Brune F, Azam P, Cook HT, Pickering MC. Treatment with human complement factor H rapidly reverses renal complement deposition in factor H-deficient mice. Kidney Int 2010;78:279-86.
16. Pickering MC, Cook HT, Warren J, et al. Uncontrolled C3 activation causes membranoproliferative glomerulonephritis in mice deficient in complement factor H. Nat Genet 2002;31:424-8.
17. Caravaca-Fontán F, Cavero T, Díaz-Encarnación M, et al. Clinical profiles and patterns of kidney disease progression in C3 glomerulopathy. Kidney360 2023;4: 659-72.
18. Tarragón B, Peleg Y, Jagannathan G, et al. C3 glomerulopathy recurs early after kidney transplantation in serial biopsies performed within the first 2 years after transplantation. Clin J Am Soc Nephrol 2024;19:1005-15.
19. Caravaca-Fontán F, Polanco N, Villacorta B, et al. Recurrence of immune complex and complement-mediated membranoproliferative glomerulonephritis in kidney transplantation. Nephrol Dial Transplant 2023;38:222-35.
20. Ueda C, Horinouchi T, Inoki Y, et al. Clinical characteristics and outcomes of immune-complex membranoproliferative glomerulonephritis and C3 glomerulopathy in Japanese children. Pediatr Nephrol 2024;39:2679-89.
21. Bomback AS, Smith RJ, Barile GR, et al. Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol 2012;7:748-56.
22. Le Quintrec M, Lapeyraque A-L, Lionet A, et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. Am J Kidney Dis 2018;72: 84-92.
23. Ruggenenti P, Daina E, Gennarini A, et al. C5 convertase blockade in membranoproliferative glomerulonephritis: a single-arm clinical trial. Am J Kidney Dis 2019;74:224-38.
24. Welte T, Arnold F, Westermann L, et al. Eculizumab as a treatment for C3 glomerulopathy: a single-center retrospective study. BMC Nephrol 2023;24:8.
25. Carrara C, Podestà MA, Abbate M, et al. Morphofunctional effects of C5 convertase blockade in immune complex-mediated membranoproliferative glomerulonephritis: report of two cases with evidence of terminal complement activation. Nephron 2020;144:195-203.
26. Medjeral-Thomas NR, Moffitt H, Lomax-Browne HJ, et al. Glomerular complement factor H-related protein 5 (FHR5) is highly prevalent in C3 glomerulopathy and associated with renal impairment. Kidney Int Rep 2019;4:1387-400.
27. Bomback AS, Herlitz LC, Kedia PP, et al. Safety and efficacy of avacopan in patients with complement 3 glomerulopathy: randomized, double-blind clinical trial. J Am Soc Nephrol 2025;36:487-99.
28. Nester C, Appel GB, Bomback AS, et al. Clinical outcomes of patients with C3G or IC-MPGN treated with the factor D inhibitor danicopan: final results from two phase 2 studies. Am J Nephrol 2022; 53:687-700.
29. FABHALTA (iptacopan) prescribing information. East Hanover, NJ: Novartis, 2025 (https://www.novartis.com/us-en/sites/novartis_us/files/fabhalta.pdf).
30. Kavanagh D, Bomback AS, Vivarelli M, et al. Oral iptacopan therapy in patients with C3 glomerulopathy: a randomised, double-blind, parallel group, multicentre, placebo-controlled, phase 3 study. Lancet 2025;406:1587-98.
31. Smith RJH, Kavanagh D, Vivarelli M, et al. Efficacy and safety of iptacopan in patients with C3 glomerulopathy: 12-month results from the phase 3 APPEAR-C3G study. Presented at the Annual Meeting of the American Society of Nephrology, San Diego, CA, October 23–27, 2024.
32. Hillmen P, Horneff R, Yeh M, Kolev M, Deschatelets P. Navigating the complement pathway to optimize PNH treatment with pegcetacoplan and other currently approved complement inhibitors. Int J Mol Sci 2024;25:9477.
33. Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014; 85:1303-9.
34. de Latour RP, Szer J, Weitz IC, et al. Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PEGASUS): 48-week follow-up of a randomised, open-label, phase 3, active-comparator, controlled trial. Lancet Haematol 2022;9(9):e648-e659.
35. Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. Blood Adv 2023;7:2468-78.
36. Mirioglu S, Cebeci E, Yazici H, et al. Prognostic factors and validation of the histologic chronicity score for C3 glomerulopathy: a registry analysis. Clin Kidney J 2024;17:sfae077.