Phase 3 Trial of Pegcetacoplan in C3G and IC-MPGN in Adults and Adolescents

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ABSTRACT

BACKGROUND: C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) generally result in glomerular C3 deposition and irreversible kidney damage. Here, we report primary results for VALIANT (NCT05067127), a double-blind, placebo-controlled trial investigating pegcetacoplan, a C3/C3b inhibitor, in adolescents and adults with native or posttransplant-recurrent C3G or IC-MPGN.

METHODS: Patients received pegcetacoplan or placebo (1:1). The primary end point was the surrogate marker of log-transformed ratio of urine protein-to-creatinine ratio (UPCR) at week 26 vs. baseline.

RESULTS: In 124 patients randomized (pegcetacoplan [n=63], placebo [n=61], proteinuria reduction (primary end point) was significantly greater with pegcetacoplan (geometric mean [95% CI] ratio of UPCR, –67.2% [–74.9 to –57.2] vs. 2.9% [–8.6 to 15.9]), a reduction of 68.1% (95% CI, 57.3 to 76.2) vs. placebo. Per hierarchical testing of 5 secondary outcomes, significantly higher percentages of the pegcetacoplan group attained a composite renal end point (estimated glomerular filtration rate [eGFR] stabilization and proteinuria reduction) (49.2% vs. 3.3%; relative risk, 14.4 [95% CI: 3.7 to 56.9]) and ≥50% proteinuria reduction (60.3% vs 4.9%; relative risk, 12.0 [4.0 to 36.1]). In patients with evaluable kidney biopsies (n=69), C3G histologic index changes did not differ significantly; subsequent end points (decrease in C3 staining; change in eGFR) were not tested. Pegcetacoplan was not associated with more adverse events compared with placebo. No infections from encapsulated bacteria occurred; one patient receiving pegcetacoplan died from Covid 19-pneumonia. No allograft rejection or loss occurred.

CONCLUSION: Pegcetacoplan significantly reduced proteinuria in patients with native or posttransplant-recurrent C3G or IC-MPGN. (Funded by Apellis Pharmaceuticals, Inc., and Sobi [Swedish Orphan Biovitrum AB]; VALIANT ClinicalTrials.gov number, NCT05067127.)

C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) are rare glomerulopathies characterized by C3 dysregulation generally leading to abnormal glomerular C3 deposition and irreversible kidney damage.[1-3] Within 10 years of diagnosis, up to 50% of patients progress to advanced kidney failure requiring dialysis or transplantation.[4,5] Recurrent C3G leads to allograft loss in up to 60% of grafts.[6,7] Although IC-MPGN has a distinct histology characterized by immunoglobulin deposition in addition to the glomerular C3 deposition of C3G,[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 C3G and IC-MPGN, preventing glomerular complement deposition and kidney failure.[10]

In two phase 2 trials, pegcetacoplan showed efficacy and safety in native and posttransplant C3G and IC-MPGN.[10,11] Here we report the primary analysis of the VALIANT trial (NCT05067127), a phase 3 trial evaluating efficacy and safety of pegcetacoplan vs. placebo in adolescents and adults with native or posttransplant recurrent C3G or IC-MPGN.

METHODS

Trial Design and Oversight

This phase 3, randomized, double-blind, placebo-controlled trial was conducted at 122 centers in 19 countries (Supplementary Appendix, **Table S1**). The study included a 10-week screening period, 26-week

randomized controlled period, 26-week open-label period, and 8-week follow-up period for patients who did not enroll in the long-term extension (VALE; NCT05809531) (**Fig. S1**).[12] Eligible patients were randomized 1:1 (using a computer-generated randomization schedule) to pegcetacoplan or placebo. Randomization was stratified by transplant status and baseline biopsy availability. At the end of the randomized controlled period, kidney biopsy was required for all adults (**Supplementary Methods**). The study protocol is provided at NEJM.org.

The sponsor (Apellis Pharmaceuticals) designed the trial, which was conducted in accordance with the International Council for Harmonisation E6 Guidelines for Good Clinical Practice, the Declaration of Helsinki, all applicable regulatory requirements, and institutional review board or independent ethics committee requirements at each site. Data were collected by trial investigators, reviewed by an independent data monitoring committee, analyzed by the sponsor, and available to all authors. The authors vouch for the data and analysis. Confidentiality agreements were in place between authors and the sponsor. Patients provided written informed consent (and assent if applicable) before participation. Apellis Pharmaceuticals and Swedish Orphan Biovitrum AB decided to publish the manuscript. Kay Square Scientific (Newtown Square, PA) provided writing assistance. All authors reviewed and approved the final manuscript.

Patients

Eligible patients were adolescents (aged 12–17 years) or adults (aged ≥18 years) with a diagnosis of primary C3G or primary IC-MPGN (established in 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 adults, active disease was defined as ≥2+ C3 immunofluorescent staining (0–3 scale) in the baseline biopsy reviewed by the central

pathologist.[13] In adolescents without a baseline biopsy, active disease was diagnosed as ≥1 of the following: plasma sC5b-9 concentration >207 ng/mL (upper limit of normal), serum C3 concentration <90 mg/dL (lower limit of normal), presence of active urine sediment, or presence of C3 nephritic factor (see **Supplementary Methods** for details and additional entry criteria). Patients with prior kidney transplants were included. Patients were required to be receiving stable (≥12 weeks before randomization) and optimized (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 dosage ≤20 mg/d or equivalent]). Those who entered while receiving immunosuppressive medications continued such treatment at stable doses. Optimal supportive care was demonstrated by consistent blood pressure control (**Fig. S2**). Anticipated dosage adjustments of immunosuppressive agents and other transplant-related medications (documented before randomization) were allowed for posttransplant patients. Vaccinations were required (**Supplementary Methods**).

All adults and adolescents weighing ≥50 kg received 1080 mg pegcetacoplan or placebo by subcutaneous injection (self-administered or given by a trained caregiver) twice weekly in addition to optimized supportive care. Adolescents weighing <50 kg received weight-adjusted dosages. Rescue treatments were permitted. See **Supplementary Methods** for dosing and rescue treatment details.

End Points and Assessments

The primary efficacy end point was the log-transformed ratio of UPCR from triplicate FMU collections at week 26 compared with baseline using an equal-weighted average over weeks 24, 25, and 26. The primary efficacy end point was further analyzed by prespecified subgroups. Key secondary efficacy end points evaluated at week 26 compared with baseline were tested hierarchically: proportion of patients who

met a composite renal end point (eGFR stabilization [≤15% reduction] and ≥50% UPCR reduction), proportion achieving ≥50% UPCR reduction, change in the activity score of the C3G histologic index[4] in patients with evaluable kidney biopsies, proportion of patients with evaluable kidney biopsies with a decrease in C3 staining ≥2 orders of magnitude in immunofluorescence intensity, and change in eGFR (see **Supplementary Methods** for details). Compliance assessments are described in **Supplementary Methods**.

Safety was evaluated throughout the study. Adverse events were documented according to 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 patients completed the week 26 assessment or discontinued. Efficacy end points were analyzed in the intent-to-treat set. The safety set included all patients who received ≥1 dose of study treatment. A fixed-sequence testing strategy was used. Longitudinal assessments for changes from baseline in continuous outcomes were analyzed using a mixed-effect model for repeated measures. Binary outcomes were analyzed using a logistic regression model to determine the P-values and odds ratios. Hierarchical testing of secondary endpoints was conducted based on logistic regression, as initially planned. Although we initially planned to report ORs, here we report RRs and 95% confidence intervals because ORs inflate the apparent magnitude of the effect in the setting of non-rare outcomes. The key secondary end point of C3G histologic index activity score was analyzed using analysis of covariance model. See **Supplementary Methods** for missing data and intercurrent event handling and sample size justification.

Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. The data cutoff for this primary analysis was June 20, 2024.

RESULTS

Patients

Between May 30, 2022, and June 20, 2024, 261 patients were screened and 124 randomized to pegcetacoplan (63 patients) or placebo (61 patients) and included in the intent-to-treat and safety sets (**Fig. S3**). Six of 124 randomized patients discontinued study treatment: two in the pegcetacoplan arm (adverse events) and four in the placebo arm (adverse event, patient withdrew consent, pregnancy, and patient noncompliance [one patient each]). At data cutoff, two patients (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 (93.7%) and 57 patients (93.4%) in the pegcetacoplan and placebo arms, respectively, completed 26 weeks of randomized treatment and continued into the open-label period. All patients in the safety set had compliance ≥80%. Two patients (placebo group) received glucocorticoid rescue treatment (**Supplementary Results**). Eight patients (pegcetacoplan, 2; placebo, 6) had intercurrent events (**Table S2**).

Baseline characteristics were similar between treatment arms for most variables, although patients who received pegcetacoplan were older and had higher proteinuria and a lower eGFR (**Table 1, Table S3**). Overall, 77.4% (96 of 124) of patients had C3G. Nine of 124 patients (7.3%) had received a kidney transplant; one posttransplant patient was an adolescent. Demographic characteristics aligned with those previously reported, supporting that the study population is representative and that findings can be generalized (**Table S4**).[14] Immunosuppressive treatment was ongoing in 71.8% (89 of 124) of patients.

Adolescents (mean age, 14.7 years; 50 with historical biopsies) comprised 44.4% (55 of 124) of patients. Patients by subgroups are found in **Supplementary Results**.

Clinical Efficacy

Primary End Point

Pegcetacoplan treatment for 26 weeks resulted in significantly greater proteinuria reduction from baseline with pegcetacoplan vs. placebo (geometric mean [95% CI] ratio of UPCR: –67.2% [–74.9 to –57.2] vs. 2.9% [–8.6 to 15.9]). This represents a proteinuria reduction of 68.1% (95% CI, 57.3 to 76.2; P<0.001) with pegcetacoplan vs. placebo (**Fig. 1A**). Proteinuria reduction with pegcetacoplan was observed as early as week four (first sample collected after treatment initiation) and sustained through week 26; proteinuria was largely unchanged with placebo (**Fig. S4, Fig. S5**). Reduction in proteinuria was broadly consistent across patient subgroups, including immunosuppressant status (**Fig. 1B, Table S5, Supplementary Results**).

Secondary End Points

Significantly more pegcetacoplan-treated patients attained the composite renal end point at week 26 vs. placebo (49.2% [31 of 63] vs. 3.3% [2 of 61]; relative risk, 14.4 [95% CI, 3.7 to 56.9]; P<0.001) (**Table 2, Fig. S6, Table S6**). This was mainly driven by improvement in proteinuria, with 60.3% (38 of 63) of patients receiving pegcetacoplan attaining a proteinuria reduction of ≥50% (key secondary end point) vs. 4.9% (three of 61) with placebo (relative risk, 12.0 [95% CI, 4.0 to 36.1]; P<0.001) (**Table 2**, **Fig. S7, Table S6**). In a post hoc analysis, proteinuria reduction with pegcetacoplan corresponded with a substantial increase in the proportion of patients with FMU UPCR <1 g/g at week 26 (7.9% at baseline vs. 50.8% at week 26) and a marked decrease in the proportion in the nephrotic range of ≥3 g/g (38.1% vs.

14.3%) (**Fig. S8**). More patients receiving pegcetacoplan achieved stable or improved eGFR (≤15% reduction) (68.3% [43 of 63] vs. 59.0% [36 of 61]).

Though there was a difference in the total C3G histologic activity score with pegcetacoplan, the key secondary end point of total C3G histologic index was not statistically significant at week 26 (**Table 2, Fig. S9**). Consequently, subsequent end points were not formally tested statistically.

The proportion of patients observed to have reduced C3 staining at week 26 (key secondary end point) was 26 of 35 (74.3%) with pegcetacoplan and 4 of 34 (11.8%) with placebo (relative risk, 6.2 [95% CI, 2.4 to 15.9]) (**Table 2**). Staining decreased to 0 intensity in 71.4% (25 of 35) of patients receiving pegcetacoplan vs. 8.8% (three of 34) with placebo (**Fig. 2, Table S6**).

From baseline to week 26, the least squares mean change in eGFR (key secondary end point) was –1.5 (95% CI, –5.9 to 2.9) mL/min/1.73 m^2 with pegcetacoplan and –7.8 (95% CI, –11.6 to –4.0) mL/min/1.73 m^2 with placebo (difference, +6.3 [95% CI, 0.5 to 12.1] mL/min/1.73 m^2]) (**Table 2**, **Fig. S10**). See **Table S7** for additional secondary end points.

Serum C3 levels appeared higher and plasma sC5b-9 appeared lower following pegcetacoplan, as compared with baseline values; C4 levels appeared similar before and after treatment (**Fig. S11**).

Safety

The incidence of unexpected adverse events during treatment was similar between the pegcetacoplan and placebo groups (84.1% [53 of 63 patients] and 93.4% [57 of 61]), as were treatment-related events (pegcetacoplan, 39.7% [25 of 63]; placebo, 42.6% [26 of 61]) (**Table 3**). Serious treatment-emergent

adverse events occurred in 6 patients per arm (pegcetacoplan, 9.5%; placebo, 9.8%). Infections accounted for the serious treatment-emergent adverse events in three (4.8%) pegcetacoplan-treated patients (Covid-19 pneumonia, influenza, pneumonia in one patient [1.6%] each) and one patient (viral infection) (1.6%) who received placebo. There was one death; a patient in the pegcetacoplan group died from respiratory failure associated with Covid-19 pneumonia (**Supplementary Results**). 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 C3G or IC-MPGN treated with pegcetacoplan in the present study had a 68.1% proteinuria reduction (vs. placebo), complete reduction of C3 staining in 71.4% of patients, and eGFR stabilization. This outcome triad aligns with the consensus recommendations for assessing C3G treatment efficacy.[13]

Proteinuria reduction has disease-specific relevance for prognosis and treatment.[2] In another study, a 50% reduction correlated with reduced rates of kidney failure (eGFR <15 mL/min/1.73 m^2),[15] and kidney failure risk was 85% lower in patients with proteinuria of <0.88 g/g 12 months from diagnosis.[14] Importantly, substantial proportions of patients in our study achieved comparable proteinuria outcomes. Additionally, abnormal glomerular C3 deposition is the pathogenic driver of kidney failure in C3G, and restoration of C3 regulation ameliorates C3G.[16,17] Early and rapid decline in eGFR is associated with a higher likelihood of kidney failure,[14,18] suggesting that eGFR stabilization with pegcetacoplan may lead to better prognosis, which would require further studies.

Pegcetacoplan showed efficacy in a broad population, including both adolescents and patients receiving immunosuppressive agents. Histologic recurrence rates up to 89% have been reported,[19,20] particularly

among adolescents, whose lifelong disease may necessitate multiple transplants.[21] Efficacy in the transplant setting is supported by this study and by the phase 2 NOBLE trial: 50% of patients had decreased C3 staining after 12 weeks of pegcetacoplan, and patients with proteinuria ≥1 g/g had a median UPCR reduction of 54%.[11]

As increased activation of complement causes C3G and IC-MPGN, treatment with targeted complement inhibition is logical. Terminal complement inhibition with the C5 inhibitor eculizumab showed limited clinical benefit in C3G or IC-MPGN, likely due to ongoing C3 activation.[22-27] Likewise, the C5a inhibitor avacopan did not show conclusive clinical benefit for C3G.[28] Danicopan, a factor D inhibitor, did not meet clinical trial end points and failed to achieve sustained complement inhibition.[29] Iptacopan, a factor B inhibitor approved to reduce proteinuria in adults with C3G,[30] demonstrated proteinuria reductions of 35% at month 6 and 37% at month 12.[31,32] C3 staining was reduced by 0.8 (12-point scale) at month 6 with iptacopan; eGFR changes were not significant.[30-32]

Pegcetacoplan is a targeted C3/C3b inhibitor that directly blocks both C3 and C5 activation by the classical, lectin and alternative pathways, inhibiting downstream effectors.[9,33] While 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 for the primary outcome results from its stopping the pathophysiologic drivers of disease. Pegcetacoplan directly affects the complement overactivation underlying C3G and IC-MPGN, reducing proteinuria independent of hemodynamic and/or anti-hypertensive treatments. Thus, pegcetacoplan may have an outcome distinct from approaches that reduce proteinuria without addressing complement dysregulation, leading to insufficient proteinuria control and potential kidney failure.[34]

Pegcetacoplan had adverse events that were as previously reported;[11,35,36] no infections by encapsulated meningococci were reported, consistent with prior trials.[33] No allograft loss or rejection w reported during the trial.

Our trial has certain limitations; one limitation is the absence of long-term pegcetacoplan efficacy and safety data in C3G and IC-MPGN. Such data are anticipated from the open-label period of this trial and the VALE extension.[12] Further, the C3G activity score has not been validated as a predictor for C3G progression.[37] Additionally, few posttransplant patients received pegcetacoplan. Finally, adolescent patients lacked follow-up biopsies and only baseline C3G etiology information was collected.

In conclusion, pegcetacoplan significantly reduced proteinuria in patients with C3G or primary IC-MPGN.

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

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Figure 1. Change From Baseline to Week 26 in UPCR

Change from baseline at week 26 in UPCR in the overall population (A) and by prespecified patient subgroups (B). This analysis was performed with the use of a mixed-effects model for repeated measures in the intent-to-treat set (all randomized patients). Baseline UPCR value was calculated as the average of the UPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day one, inclusive. The changes in UPCR were calculated using the geometric mean ratio. Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. **** P<0.001. Intent-to-treat set (all randomized patients). *IS status was based on "immunosuppressants" and/or "corticosteroids for systemic use" per Anatomical Therapeutic Chemical level 2.

C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; FMU, first-morning spot urine; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IS, immunosuppressant; UPCR, urine protein-to-creatinine ratio.

Figure 2. C3 Staining in Kidney Biopsies

Shifts in C3 staining in adult patients with evaluable kidney biopsies (A) and representative images of a +3 to 0 C3 staining shift and electron microscopy in a patient with C3G and a native kidney after 26 weeks of pegcetacoplan treatment (B).

Shift analysis performed using data from adults with evaluable biopsies in the intent-to-treat set.

Renal biopsy findings from a representative patient, pretreatment (top row) and post-treatment (bottom row). Top row, left column: mild mesangial expansion (periodic acid-Schiff stain, original magnification 400×); top row, right column: diffuse capillary loop and mesangial staining (fluorescein-conjugated anti-human C3, original magnification 400×); bottom row, left column: mesangial expansion (hematoxylin

and eosin stain, original magnification 400×); bottom row, middle column: essentially negative staining (fluorescein-conjugated anti-human C3, original magnification 400×).

Note: IF staining is performed with antibodies against C3. This antibody does not interfere with the activity of pegcetacoplan.

C3G, C3 glomerulopathy; IF, immunofluorescence; LS, least squares.

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	Pegcetacoplan (n = 63)	Placebo (n = 61)	Overall (N = 124)
Age group			
Adolescent (12–17 yr)/adult (≥18 yr) — no. (%)	28 (44.4)/35 (55.6)	27 (44.3)/34 (55.7)	55 (44.4)/69 (55.6)
Adolescents/adults, mean (SD), yr	14.6 (1.7)/39.1 (15.9)	14.8 (1.8)/30.6 (15.9)	14.7 (1.7)/35.0 (16.4)
Female sex — no. (%)	37 (58.7)	33 (54.1)	70 (56.5)
Race — no. (%)			
White	45 (71.4)	46 (75.4)	91 (73.4)
Asian	9 (14.3)	9 (14.8)	18 (14.5)
American Indian or Alaskan Native	1 (1.6)	0	1 (0.8)
Black or African American	1 (1.6)	0	1 (0.8)
Other[†]	7 (11.1)	6 (9.8)	13 (10.5)
Underlying disease based on screening biopsy — no. (%)			
C3G	51 (81.0)	45 (73.8)	96 (77.4)
Primary IC-MPGN	12 (19.0)	16 (26.2)	28 (22.6)
Prior kidney transplant — no. (%)	5 (7.9)	4 (6.6)	9 (7.3)
Baseline triplicate first-morning spot urine protein-to-creatinine ratio, mg/g			
Median (range)	2389.2 (713.6–11 418.0)	1815.6 (783.4–10 439.0)	2031.3 (713.6–11 418.0)
Baseline estimated glomerular filtration rate, median (range), mL/min/1.73 m^2	78.0 (25–161)	91.0 (24–156)	85.5 (24–161)
Concomitant therapies — no. (%)[†]			
Renin-angiotensin system blocking agents	57 (90.5)	56 (91.8)	113 (91.1)
Immunosuppressants	47 (74.6)	42 (68.9)	89 (71.8)
Systemic glucocorticoids	25 (39.7)	24 (39.3)	49 (39.5)
Sodium-glucose cotransporter-2 inhibitors[#]	7 (11.1)	6 (9.8)	13 (10.5)

Abbreviations: C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; IC-MPGN, immune-complex membranoproliferative glomerulonephritis.

This table includes patients in the intent-to-treat set defined as all randomized patients, unless otherwise specified.

[†]Includes patients in the safety set defined as all patients who received ≥1 dose of study treatment.

[‡]Includes dapagliflozin, dapagliflozin propanediol monohydrate, and empagliflozin.]

Table 2. Key Secondary End Points

End point	Pegcetacoplan	Placebo	Pegcetacoplan vs. placebo (95% CI)
Patients achieving the composite renal end point (eGFR stabilization [⩽15% reduction] and ⩾50% UPCR reduction) at week 26, n (%)	N=63 31 (49.2)	N=61 2 (3.3)	Relative risk* 14.4 (3.7, 56.9) P<0.001†
Patients achieving ⩾50% reduction in FMU UPCR at week 26, n (%)	N=63 38 (60.3)	N=61 3 (4.9)	Relative risk* 12.0 (4.0, 36.1) P<0.001†
Change in the activity score of the C3G histologic index score‡ from baseline at week 26 (LS mean, 95% CI)§	N=35 –3.5 (–4.7, –2.2)	N=34 –2.5 (–3.8, –1.2)	Adjusted mean difference –1.0 (–2.8, 0.8) P=0.28
Patients achieving a decrease in C3 staining of ⩾2 orders of magnitude at week 26, n (%)§	N=35 26 (74.3)	N=34 4 (11.8)	Relative risk* 6.2 (2.4, 15.9)
Change in eGFR from baseline at week 26 (LS mean, 95% CI), mL/min/1.75 m^2	N=63 –1.5 (–5.9, –2.9)	N=61 –7.8 (–11.6, –4.0)	Least squares mean change (95% CI) 6.3 (0.5, 12.1)

Key secondary end points. A fixed-sequence testing strategy was used. Statistical significance of the first secondary endpoint was evaluated only if statistical significance was achieved with the prespecified primary analysis of the primary endpoint. Hierarchical testing of secondary endpoints was conducted based on logistic regression, as initially planned. Although we also initially planned to report ORs, here we report RRs and 95% confidence intervals because ORs inflate the apparent magnitude of the effect in the setting of non-rare outcomes.

*Covariate-adjusted relative risks and corresponding 95% confidence intervals are reported for binary outcomes using modified Poisson regression model as post-hoc analysis.

†P-values are based on logistic regression/hypothesis testing for the odds ratios; shown in **Table S6**.

‡Kidney biopsy end points were only evaluated for adult patients.

[§]The C3G histologic index activity score measures disease activity using a semiquantitative scale of 0 to 3 to assess 7 markers of C3G activity. Activity scores range from 0 (lowest activity) to 21 (highest activity).[4]

C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio.

Table 3. Treatment-Emergent Adverse Events

Patients	**Pegcetacoplan (n = 63)**	**Placebo (n = 61)**
TEAEs	53 (84.1)	57 (93.4)
Treatment-related	25 (39.7)	26 (42.6)
Severe TEAEs	3 (4.8)	4 (6.6)
Serious TEAEs*	6 (9.5)	6 (9.8)
Covid-19 pneumonia	1 (1.6)	0
Influenza	1 (1.6)	0
Pneumonia	1 (1.6)	0
Viral infection	0	1 (1.6)
Acute renal injury	1 (1.6)	2 (3.3)
Nephrotic syndrome	1 (1.6)	0
Proteinuria	0	1 (1.6)
Tubulointerstitial nephritis	0	1 (1.6)
Pyrexia	1 (1.6)	0
Respiratory failure	1 (1.6)	0
Hypertension	1 (1.6)	0
Vomiting	0	1 (1.6)
Blood creatinine increased	0	1 (1.6)
Spontaneous abortion	0	1 (1.6)
Pregnancy	0	1 (1.6)
TEAEs leading to study discontinuation	1 (1.6)	1 (1.6)
Deaths[†]	1 (1.6)	0

TEAE, treatment-emergent adverse event.

Safety set defined as all patients who received ≥1 dose of study treatment.

*If a patient experienced multiple occurrences of a TEAE, the patient is counted only once in the patient count, whereas all occurrences contribute to the total event count.

[†]Death due to Covid-19 pneumonia.

Figure 1

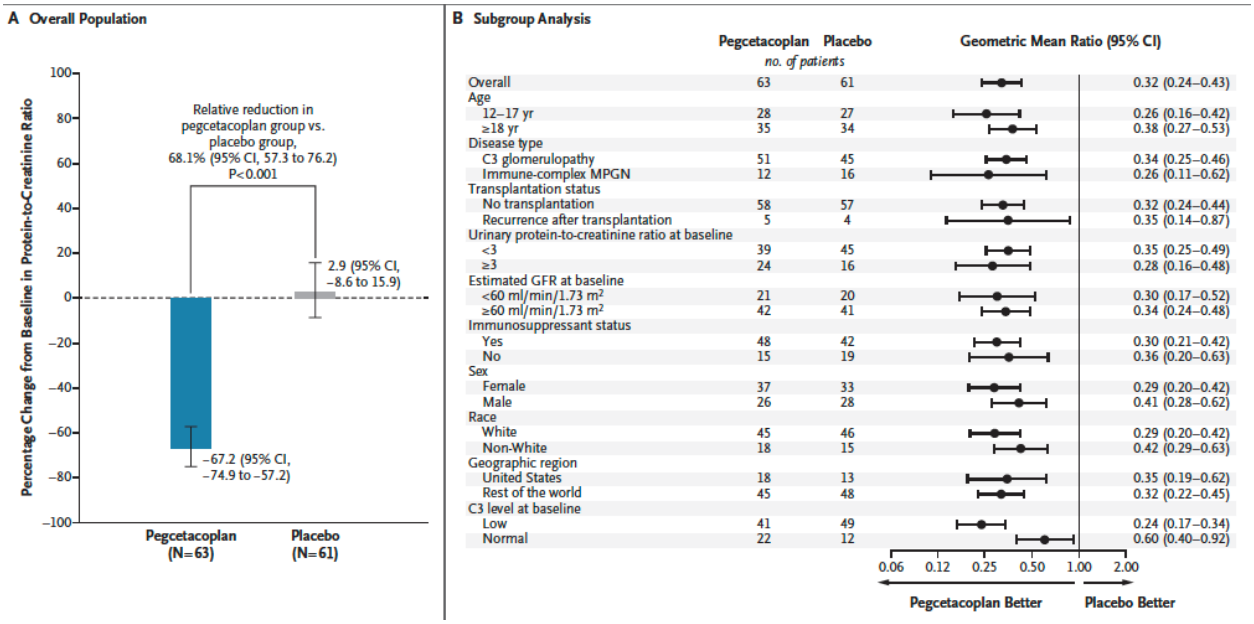
A Overall Population
Percentage Change from Baseline in Protein-to-Creatinine Ratio
100
80
60
40
20
0
−20
−40
−60
−80
−100
Relative reduction in pegcetacoplan group vs. placebo group, 68.1% (95% CI, 57.3 to 76.2) P<0.001
2.9 (95% CI, −8.6 to 15.9)
−67.2 (95% CI, −74.9 to −57.2)
Pegcetacoplan (N=63)
Placebo (N=61)
B Subgroup Analysis
Pegcetacoplan
Placebo
no. of patients
Geometric Mean Ratio (95% CI)
Overall 63 61 0.32 (0.24–0.43)
Age
12–17 yr 28 27 0.26 (0.16–0.42)
≥18 yr 35 34 0.38 (0.27–0.53)
Disease type
C3 glomerulopathy 51 45 0.34 (0.25–0.46)
Immune-complex MPGN 12 16 0.26 (0.11–0.62)
Transplantation status
No transplantation 58 57 0.32 (0.24–0.44)
Recurrence after transplantation 5 4 0.35 (0.14–0.87)
Urinary protein-to-creatinine ratio at baseline
<3 39 45 0.35 (0.25–0.49)
≥3 24 16 0.28 (0.16–0.48)
Estimated GFR at baseline
<60 ml/min/1.73 m² 21 20 0.30 (0.17–0.52)
≥60 ml/min/1.73 m² 42 41 0.34 (0.24–0.48)
Immunosuppressant status
Yes 48 42 0.30 (0.21–0.42)
No 15 19 0.36 (0.20–0.63)
Sex
Female 37 33 0.29 (0.20–0.42)
Male 26 28 0.41 (0.28–0.62)
Race
White 45 46 0.29 (0.20–0.42)
Non-White 18 15 0.42 (0.29–0.63)
Geographic region
United States 18 13 0.35 (0.19–0.62)
Rest of the world 45 48 0.32 (0.22–0.45)
C3 level at baseline
Low 41 49 0.24 (0.17–0.34)
Normal 22 12 0.60 (0.40–0.92)
0.06
0.12
0.25
0.50
1.00
2.00
Pegcetacoplan Better
Placebo Better

Figure 2

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