Efficacy of pegcetacoplan in patients with lower baseline proteinuria: a subgroup analysis from the VALIANT trial

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CONCLUSIONS

- **In patients with C3G or primary IC-MPGN and baseline proteinuria levels ≤1.5 g/g, pegcetacoplan demonstrated clinically meaningful improvements in relevant outcomes with effects similar to those reported in the overall VALIANT population.**
- **No new safety signals were identified.**
- **These findings highlight the potential benefit of pegcetacoplan treatment in patients with C3G or primary IC-MPGN who have milder clinical phenotypes.**

BACKGROUND

- Proteinuria is a key prognostic marker in C3 glomerulopathy (C3G) and primary (idiopathic) immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) – two rare, complement-mediated kidney diseases.[1,2]
- In the Phase 3 VALIANT study, pegcetacoplan – a C3/C3b inhibitor – achieved a 68.1% (95% confidence interval [CI]: 57.3, 76.2) relative reduction in proteinuria compared with placebo in patients with C3G or primary IC-MPGN, and was well tolerated.[3]
- Patients with lower baseline levels of proteinuria (i.e., <1.0 g/g) were excluded from the VALIANT study and, consequently, evidence of the effectiveness of pegcetacoplan in this subgroup is limited.[3]
- Although patients with lower levels of proteinuria are generally considered lower risk, recent studies suggest that even modest proteinuria may confer a substantial risk of kidney function decline in C3G and primary IC-MPGN.[1,2]
  - Such evidence supports the need to evaluate therapeutic interventions in patients with lower baseline proteinuria.

OBJECTIVE

- **To evaluate the efficacy and safety of pegcetacoplan in a *post hoc* analysis of the VALIANT data focusing on patients who had proteinuria levels ≤1.5 g/g at baseline.**

METHODS

- VALIANT enrolled patients aged ≥12 years with biopsy-confirmed C3G or primary IC-MPGN who had proteinuria ≥1 g/day on screening urine collection and urine protein-to-creatinine ratio (UPCR) ≥1 g/g in two or more first-morning urine (FMU) samples.[3]
- Patients were randomized 1:1 to receive ≤1080 mg twice-weekly doses of subcutaneous (SC) pegcetacoplan[a] or placebo during the 26-week double-blind, placebo-controlled period; both groups also received stable, optimized supportive care.[b,3]
- The primary endpoint was the log-transformed ratio of UPCR at Week 26 compared with baseline (i.e., start of the 26-week double-blind period).[3]
- This *post hoc* analysis evaluated data from patients in the VALIANT trial who had proteinuria ≤1.5 g/g at baseline (FMU UPCR); the following endpoints/outcomes were assessed at Week 26:
  - change in FMU UPCR (log-transformed) from baseline
  - proportion of patients with ≥50% reduction in FMU UPCR from baseline
  - proportion of patients who achieved absolute FMU UPCR thresholds ≤0.5 g/g (remission) and ≤0.2 g/g (normalization)
  - proportion of adult patients showing decreased C3 staining on kidney biopsy[c]
  - change in estimated glomerular filtration rate (eGFR) from baseline
  - treatment-emergent adverse events (TEAEs) occurring throughout the study.

RESULTS

Baseline characteristics

- In total, 40 patients had FMU UPCR levels ≤1.5 g/g at baseline and were included in the analysis; 15 patients in the pegcetacoplan group (8 adolescents [12–17 years]; 7 adults [≥18 years]) and 25 patients in the placebo group (10 adolescents; 15 adults).
- Baseline characteristics were well balanced across treatment groups (**Table 1**), as observed for the overall VALIANT study population.[3]
  - The mean age was approximately 26 years and patient age ranged from 12 to 74 years; patients were diagnosed with C3G or primary IC-MPGN for a mean of <4 years before study entry.
  - The median FMU UPCR was 1.1 g/g; in the overall VALIANT study population, the median FMU UPCR was 2.0 g/g.[3]

Table 1. Patient characteristics at baseline

	Pegcetacoplan (n=15)[a]	Placebo (n=25)[a]
Age, mean (SD), years	26.9 (17.7)	25.3 (15.6)
Sex, female, n (%)	9 (60.0)	9 (36.0)
Race, n (%)		
White	9 (60.0)	20 (80.0)
Asian	4 (26.7)	3 (12.0)
Other[b]	2 (13.3)	2 (8.0)
BMI, mean (SD), kg/m²	22.7 (5.9)	22.0 (4.8)
24-hr UPCR, median (min, max), g/g	1.6 (0.6–2.5)	1.6 (0.7–4.0)
Triplicate FMU UPCR, median (min, max), g/g[c]	1.1 (0.7–1.4)	1.1 (0.8–1.5)
eGFR, mean (SD), mL/min/1.73 m²	89.0 (36.0)	85.7 (39.4)
Underlying disease based on screening biopsy, n (%)		
C3G	14 (93.3)	20 (80.0)
C3GN	12 (80.0)	17 (68.0)
DDD	2 (13.3)	3 (12.0)
Undetermined	0 (0.0)	0 (0.0)
Primary IC-MPGN	1 (6.7)	5 (20.0)
Time since diagnosis, mean (SD), years	3.5 (2.6)	3.9 (4.1)
Patients with prior kidney transplant(s), n (%)	1 (6.7)	3 (12.0)
Patients receiving immunosuppressant treatment, n (%)	11 (73.3)	19 (76.0)

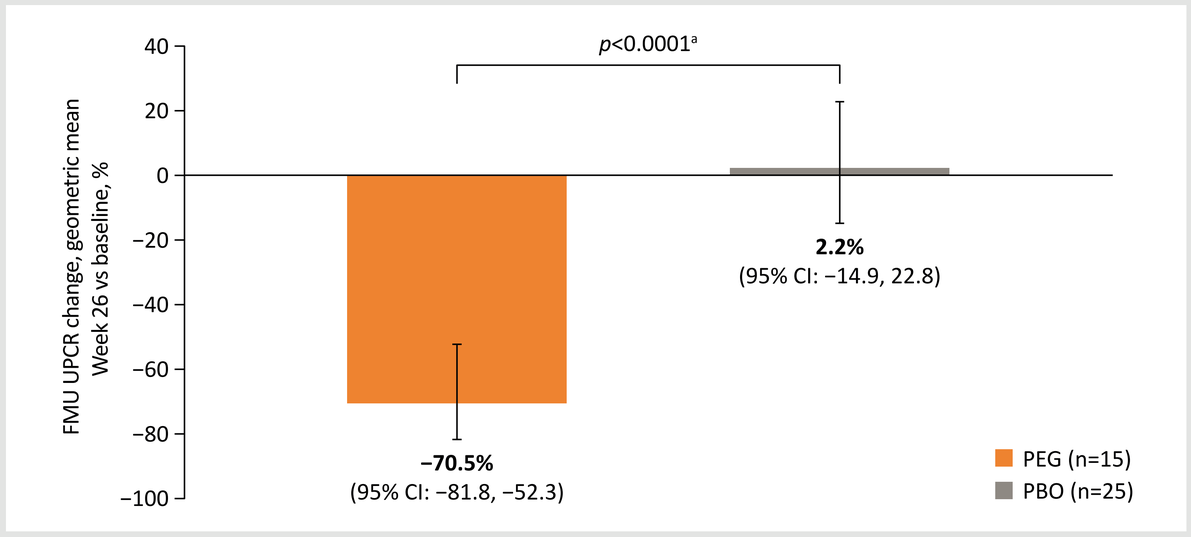
Data presented for the ITT set (all randomized patients).
[a]Pegcetacoplan: 8 adolescents and 7 adults; placebo: 10 adolescents and 15 adults; [b]none of the patients were American Indian or Alaskan Native, Black or African American, or Native Hawaiian or other Pacific Islander; [c]baseline UPCR is the result of the average of up to nine values collected.
BMI, body mass index; C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; FMU, first-morning urine; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; ITT, intent to treat; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

[a]All adults and adolescents weighing ≥50 kg self-administered (or had administered by a trained caregiver) 1080 mg/20 mL twice weekly. Adolescent patients weighing 30 to <35 kg received 540 mg/10 mL for the first two doses, then 648 mg/12 mL twice weekly. Adolescent patients weighing 35 to <50 kg received 648 mg/12 mL for the first dose, then 810 mg/15 mL twice weekly. [b]Stable, optimized antiproteinuric regimens were permitted: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, sodium–glucose cotransporter-2 inhibitors, mycophenolate mofetil, and corticosteroids (prednisone ≤20 mg/day or equivalent). [c]Decrease in C3 staining defined as a decrease in intensity of ≥2 orders of magnitude from baseline; adolescents were excluded as they were not required to provide post-screening biopsies.

Efficacy

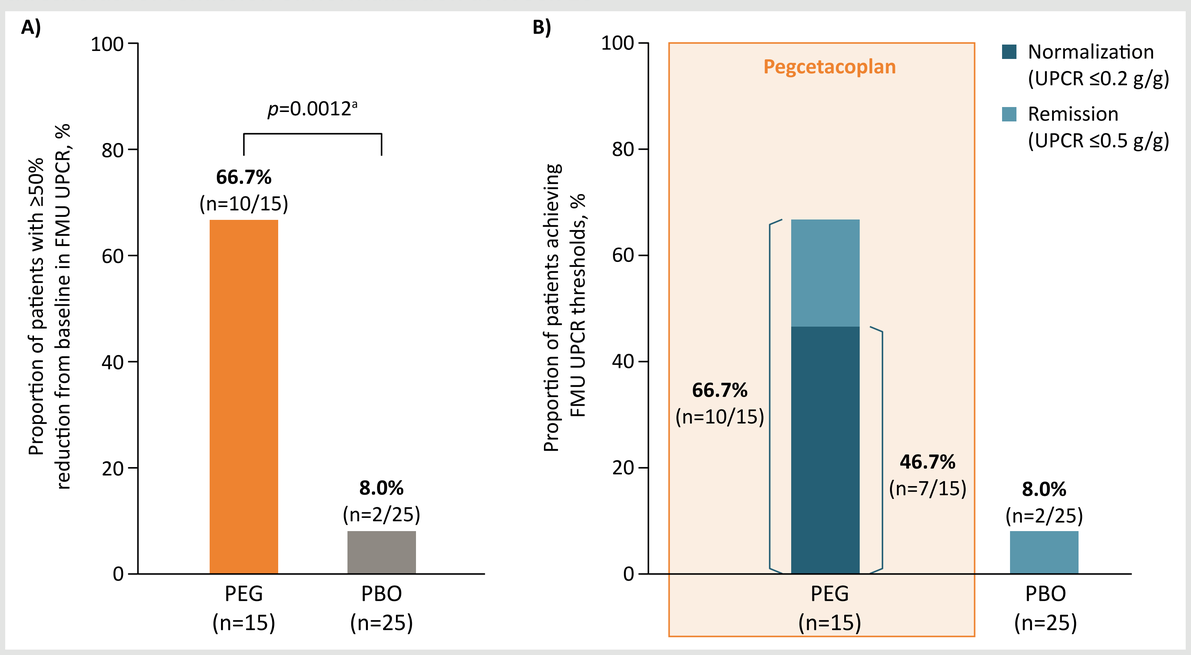
- At Week 26, the geometric mean (95% CI) change from baseline in FMU UPCR was −70.5% in the pegcetacoplan group and 2.2% in the placebo group, yielding a 71.2% relative reduction in FMU UPCR with pegcetacoplan versus placebo (geometric mean ratio [95% CI]: 0.288 [0.172, 0.483]; **Figure 1**).
- The proportion of patients achieving a ≥50% reduction in FMU UPCR from baseline to Week 26 was statistically significantly greater in the pegcetacoplan group compared with the placebo group (odds ratio [95% CI]: 26.7 [3.7, 193.0], p=0.0012; **Figure 2A**).
- The proportions of patients who reached the FMU UPCR thresholds for remission (≤0.5 g/g) and normalization (≤0.2 g/g) were 66.7% (n=10/15) and 46.7% (n=7/15) in the pegcetacoplan group, respectively, and 8.0% (n=2/25) and 0.0% in the placebo group, respectively (**Figure 2B**).
- The proportion of patients who showed a decrease in C3 staining[c] from baseline to Week 26 was 57.1% (n=4/7) in the pegcetacoplan group and 20.0% (n=3/15) in the placebo group (odds ratio [95% CI]: 6.5 [0.3, 124.3]).
- The least squares (LS) mean (95% CI) change from baseline to Week 26 in eGFR was −2.7 (−8.2, 2.8) mL/min/1.73 m² in the pegcetacoplan group and −4.6 (−9.9, 0.6) mL/min/1.73 m² in the placebo group (LS mean difference [95% CI]: 1.9 [−5.3, 9.2] mL/min/1.73 m²).
- These *post hoc* efficacy findings broadly align with the overall VALIANT study population.[3]

Figure 1. Change in proteinuria from baseline at Week 26



Data presented for the ITT set (all randomized patients).
[a]MMRM was used for this analysis; treatment group, visit, disease type, baseline immunosuppressant use, stratification factors, and visit-by-treatment group interactions were included as fixed categorical effects and baseline values were included as a continuous, fixed covariate. Percentages were calculated by converting geometric means, which were estimated by the exponentiated LS means and differences. LS means were estimated using a composite contrast of equal-weighted averages over Weeks 24–26.
CI, confidence interval; FMU, first-morning urine; ITT, intent to treat; LS, least squares; MMRM, mixed model for repeated measures; PBO, placebo; PEG, pegcetacoplan; UPCR, urine protein-to-creatinine ratio.

Figure 2. Proportion of patients who achieved (A) a reduction of ≥50% from baseline in UPCR or (B) UPCR thresholds for remission or normalization at Week 26



Data presented for the ITT set (all randomized patients).
[a]Estimated using a logistic model for the odds ratio, with treatment group as the independent variable and adjusted for baseline log-transformed UPCR values, disease type, and stratification factors.
FMU, first-morning urine; ITT, intent to treat; PBO, placebo; PEG, pegcetacoplan; UPCR, urine protein-to-creatinine ratio.

Safety

- TEAE frequency was similar between the pegcetacoplan and placebo groups; no encapsulated meningococcal infections were reported (**Table 2**).

Table 2. TEAEs reported in >10% of patients in the pegcetacoplan group

Proportion of patients reporting TEAEs, n (%)	Pegcetacoplan (n=15)	Placebo (n=25)
Any TEAE	12 (80.0)	22 (88.0)
Pyrexia	3 (20.0)	2 (8.0)
Abdominal pain	3 (20.0)	2 (8.0)
Diarrhea	2 (13.3)	4 (16.0)
Influenza	2 (13.3)	2 (8.0)
Nasopharyngitis	2 (13.3)	2 (8.0)
Upper abdominal pain	2 (13.3)	0 (0.0)
Lymphadenopathy	2 (13.3)	0 (0.0)
Paresthesia	2 (13.3)	0 (0.0)
Pruritus	2 (13.3)	0 (0.0)
Cough	2 (13.3)	0 (0.0)
Contusion	2 (13.3)	0 (0.0)

Data presented for the safety set (all patients who had received at least one dose of pegcetacoplan or placebo).
TEAE, treatment-emergent adverse event.

Limitation

- Small patient numbers in the *post hoc* analysis limit interpretation of results (for eGFR and C3 staining, in particular).

References: **1.** Caravaca-Fontán F, *et al. Kidney Int Rep.* 2025;10:1223–36. **2.** Caravaca-Fontán F, *et al. Nephrol Dial Transplant.* 2022;37:1270–80. **3.** Fakhouri F, *et al. N Engl J Med.* 2025;393:2210–20.

Abbreviations: BMI, body mass index; C3, complement 3 protein; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; CI, confidence interval; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; FMU, first-morning urine; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; ITT, intent to treat; LS, least squares; MMRM, mixed model for repeated measures; PBO, placebo; PEG, pegcetacoplan; SC, subcutaneous; SD, standard deviation; TEAE, treatment-emergent adverse event; UPCR, urine protein-to-creatinine ratio.

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