# VALIANT: Randomised, multicentre, double-blind, placebo-controlled, phase 3 trial of pegcetacoplan for patients with native or post-transplant recurrent C3G or primary (idiopathic) IC-MPGN

P-120

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## CONCLUSIONS

Pegcetacoplan was efficacious and well tolerated in the phase 3 VALIANT trial in patients (≥12 years) with complement 3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN):

- After 52 weeks of treatment, patients receiving pegcetacoplan showed a **67.2% reduction** in proteinuria from baseline.
- **Estimated glomerular filtration rate (eGFR) remained stable** among patients who received pegcetagoplan for 52 weeks **(mean change from baseline [CfB]: −3.7 ml/min/1.73 m²)**.
- Pegcetacoplan was **well tolerated, with no new safety signals. Four infections caused by encapsulated bacteria** were reported during the open-label period (OLP); **only one case of pneumococcal pneumonia was considered serious.**

## BACKGROUND

- Pegcetacoplan is a targeted complement 3 (C3) and C3b inhibitor that acts centrally to block C3 dysregulation and downstream activation of the complement cascade in C3G and primary IC-MPGN.[1,2]
- VALIANT evaluated the use of pegcetacoplan for treatment of C3G and primary IC-MPGN.[3,4]
- Week 26 data for the VALIANT phase 3 study (NCT05067127) demonstrated a slowing of disease progression with pegcetacoplan in adolescent and adult patients with C3G or primary IC-MPGN. Results were published previously.[5]

## OBJECTIVE

- Here, we report the 52-week data from VALIANT for the efficacy and safety of pegcetacoplan treatment in patients with C3G or primary IC-MPGN.

## METHODS

- Adolescent (12–17 years) and adult (≥18 years) patients were randomised 1:1 to receive ≤1080 mg pegcetacoplan subcutaneously (SC) twice weekly,* or placebo for 26 weeks.
- The 26-week, double-blind, randomised controlled period (RCP) was followed by a 26-week OLP during which all patients received pegcetacoplan ≤1080 mg SC twice weekly.* In both arms, patients also received stable, optimised supportive care.† Patients who completed VALIANT were eligible to enter the VALE extension study.[6]
- Study eligibility criteria have been reported previously.[5]
- Endpoints assessed from baseline to weeks 26 and 52 were:
  - CfB in the log-transformed ratio of urine protein-to-creatinine ratio (UPCR).
  - Proportion of patients achieving a composite renal endpoint (defined as stable or improved eGFR compared with the baseline visit [≤15% reduction in eGFR] and a ≥50% reduction in UPCR compared with the baseline visit).
  - Proportion of patients with a reduction of ≥50% in UPCR.
  - CfB in eGFR.
  - Treatment-emergent adverse events (TEAEs).

## RESULTS

### Patient characteristics

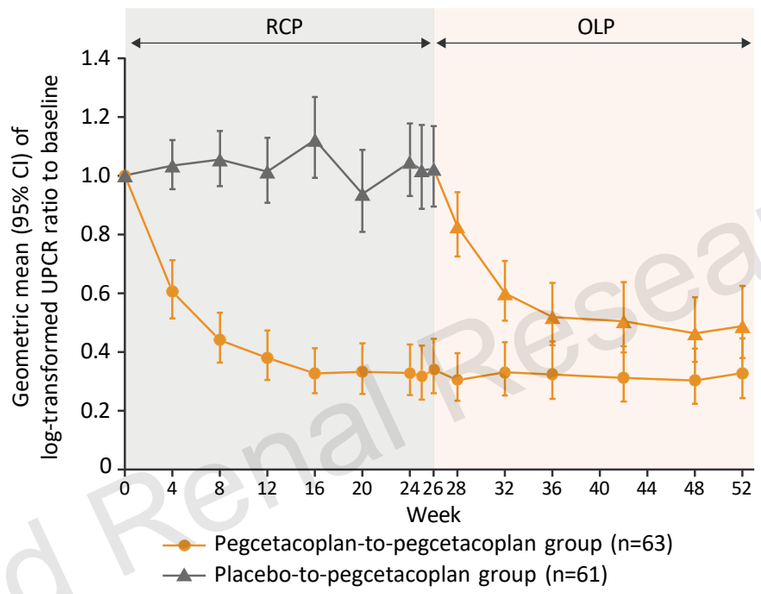
- Baseline demographics and clinical characteristics of the 26-week VALIANT study have been published previously.[5]
- VALIANT included a broad patient population aged ≥12 years, with or without previous renal transplant, and diagnosed with C3G or primary (idiopathic) IC-MPGN.
- Most patients in the pegcetacoplan group were adults; patients were, on average, 3.6 years from diagnosis and 7.9% had experienced a recurrence of C3G or IC-MPGN after transplant.
- In the placebo group, 57 (93.4%) patients completed the RCP and 55 (90.2%) completed the OLP.
- In the pegcetacoplan group, 61 (96.8%) patients completed the RCP and 59 (93.7%) completed the OLP.

### Efficacy

#### Proteinuria reduction

- In pegcetacoplan-treated patients, proteinuria reductions were observed as early as week 4 with a statistically significant and clinically meaningful reduction at week 26 vs placebo (relative reduction‡ [95% confidence interval (CI)] vs placebo: −68.1% [57.3, 76.2], *P*<0.0001) (**Figure 1**); results were consistent across disease type, age and transplant status subgroups.[5]
- This trend for reduced proteinuria was maintained until week 52 (mean CfB in the pegcetacoplan-to-pegcetacoplan group: −67.2%) (**Figure 1**).

**Figure 1:** Change in proteinuria




CI, confidence interval; OLP, open-label period; RCP, randomised controlled period; UPCR, urine protein-to-creatinine ratio.

**Figure 3:** Proportion of patients with ≥50% proteinuria reduction

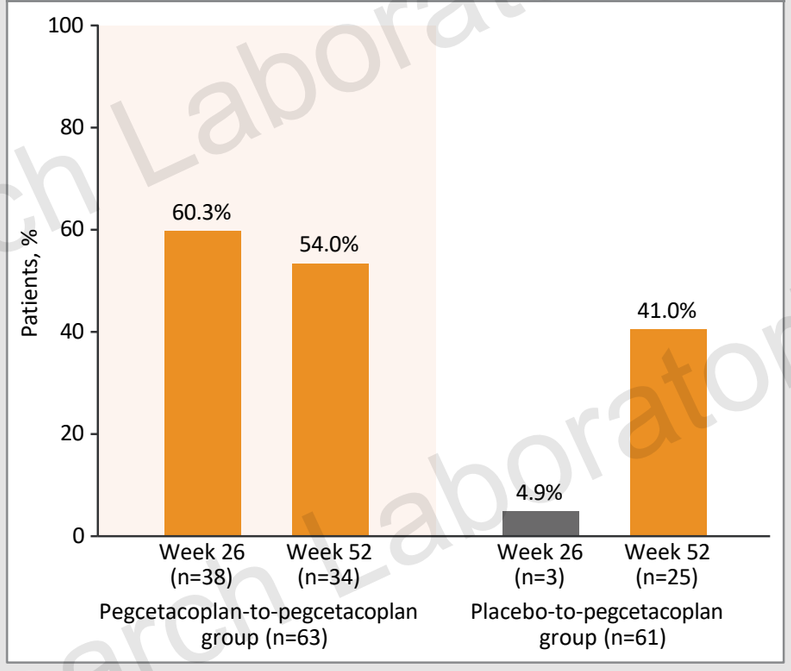
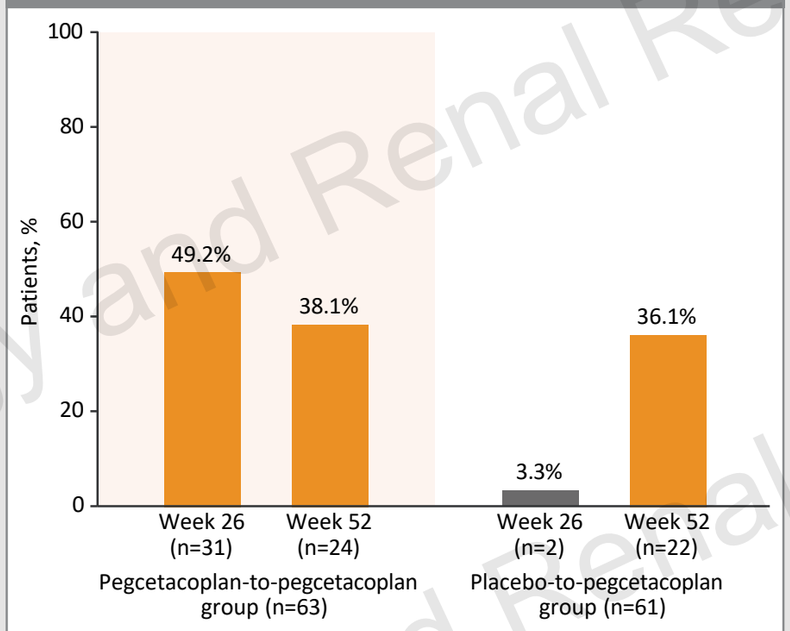
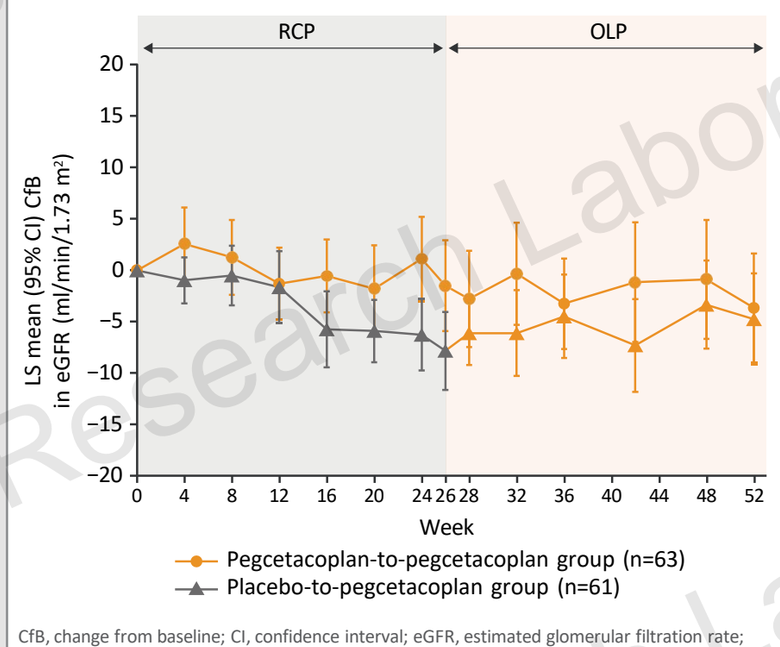



**Figure 2:** Proportion of patients who met the composite renal endpoint (≤15% reduction in eGFR and ≥50% reduction in UPCR)




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

**Figure 4:** Change in eGFR




CfB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares; OLP, open-label period; RCP, randomised controlled period.

- In the placebo-to-pegcetacoplan group, patients achieved similar proteinuria reduction after 26 weeks of pegcetacoplan treatment (mean CfB at week 52: −51.3%) (**Figure 1**).

#### Composite renal endpoint

- At week 26, the composite renal endpoint was achieved by significantly more patients receiving pegcetacoplan vs placebo (31 [49.2%] vs 2 [3.3%]; *P*≤0.0001)[5] (**Figure 2**).
- At week 52, the composite renal endpoint was met by 38.1% (n=24) of patients in the pegcetacoplan-to-pegcetacoplan group and by 36.0% (n=22) in the placebo-to-pegcetacoplan group (**Figure 2**).

#### UPCR ≥50% reduction

- At week 26, ≥50% proteinuria reduction was achieved by significantly more patients on pegcetacoplan vs placebo (38 [60.3%]) vs (3 [4.9%]; *P*<0.0001)[5] (**Figure 3**).
- At week 52, this endpoint was achieved by 54.0% (n=34) of patients in the pegcetacoplan-to-pegcetacoplan group and 41.0% (n=25) in the placebo-to-pegcetacoplan group (**Figure 3**).

#### eGFR

- At week 26, pegcetacoplan stabilised eGFR vs placebo (least squares [LS] mean CfB [95% CI]: −1.5 [−5.9, 2.9] vs −7.8 [−11.6, −4.0]; nominal *P*<0.05), equating to a difference of +6.3 ml/min/1.73 m² (nominal *P*=0.03)[5] (**Figure 4**).
- This trend was sustained through week 52 (mean CfB in the pegcetacoplan-to-pegcetacoplan group: −3.7 ml/min/1.73 m²) (**Figure 4**).
- In the placebo-to-pegcetacoplan group, eGFR stabilisation was observed during the 26 weeks of pegcetacoplan treatment (mean CfB at week 52: −4.7 ml/min/1.73 m²) (**Figure 4**).

#### Adherence

- High adherence rates (≥90%) were observed in most patients.
  - Pegcetacoplan-to-pegcetacoplan group: 96.7% (n=59).
  - Placebo-to-pegcetacoplan group: 96.5% (n=55).

### Safety

- TEAE frequency and severity were comparable between treatment arms (**Table 1**). Most TEAEs during the OLP were mild (45 [38.1%]) or moderate (36 [30.5%]).
- Infusion-related TEAEs decreased from the RCP to the OLP for the pegcetacoplan-to-pegcetacoplan group, suggesting that tolerability improved with patient experience.
- During the OLP:
  - No deaths were reported.
  - No allograft loss was reported.
  - One patient (1.6%) in the pegcetacoplan-to-pegcetacoplan group experienced a mild rejection episode, which was deemed not related to pegcetacoplan.
- No infections caused by encapsulated bacteria were reported during the RCP.
  - Four infections caused by encapsulated bacteria were reported during the OLP: two cases of pneumococcal pneumonia, one case of streptococcal pharyngitis, and one urinary tract infection caused by *Escherichia*.
  - One case of pneumococcal pneumonia was considered serious.

**Table 1:** TEAEs by treatment arm and study phase

| Event, n (%) | RCP | OLP | |
|---|---|---|---|
| | Pegcetacoplan (n=63) | Pegcetacoplan-to-pegcetacoplan (n=61) | Placebo-to-pegcetacoplan (n=57) |
| Any TEAE | 54 (85.7) | 47 (77.0) | 42 (73.7) |
| Maximum severity | | | |
| Mild | 26 (41.3) | 25 (41.0) | 20 (35.1) |
| Moderate | 25 (39.7) | 19 (31.1) | 17 (29.8) |
| Severe | 3 (4.8) | 3 (4.9) | 5 (8.8) |
| Treatment-related TEAE | 27 (42.9) | 10 (16.4) | 19 (33.3) |
| Infusion-related TEAE | 21 (33.3) | 6 (9.8) | 12 (21.1) |
| Serious TEAE | 6 (9.5) | 6 (9.8) | 4 (7.0) |
| TEAE leading to treatment withdrawal | 2 (3.2) | 2 (3.3) | 2 (3.5) |
| TEAE leading to dose interruption | 8 (12.7) | 7 (11.5) | 6 (10.5) |
| TEAE leading to study discontinuation | 1 (1.6) | 2 (3.3) | 2 (3.5) |
| TEAE leading to death | 1 (1.6) | 0 (0.0) | 0 (0.0) |
| Rejection episode | 0 (0.0) | 1 (1.6) | 0 (0.0) |
| Graft loss | 0 (0.0) | 0 (0.0) | 0 (0.0) |

OLP, open-label period; RCP, randomised controlled period; TEAE, treatment-emergent adverse event.

*All adolescents and adults weighing ≥50 kg self-administered 1080 mg/20 ml. Adolescent patients weighing 30–34 kg received 540 mg/10 ml for the first two doses, and 648 mg/12 ml thereafter. Adolescent patients weighing 35–49 kg received 648 mg/12 ml for the first dose, and 810 mg/15 ml thereafter. †Stable, optimised antiproteinuric regimens: ACEis, ARBs, SGLT2is, MMF, and corticosteroids (prednisone ≤20 mg/day or equivalent) were permitted. ‡Percentages calculated by converting the ratio of geometric means to percentages.

**Abbreviations:** ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C3, complement 3; C3G, complement 3 glomerulopathy; CfB, change from baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; LS, least squares; MMF, mycophenolate mofetil; OLP, open-label period; RCP, randomised controlled period; SC, subcutaneous; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TEAE, treatment-emergent adverse event; UPCR, urine protein-to-creatinine ratio.

**References:** 1. ASPAVELI Summary of Product Characteristics 2024. 2. Lamers C, *et al. Nat Commun* 2022;13:5519. 3. Dixon BP, *et al.* ASN Kidney Week 2023, Nov 2–5, 2023. Abstract INFO12-SA. 4. ClinicalTrials.gov. VALIANT. https://clinicaltrials.gov/study/NCT05067127. Accessed 4 August 2025. 5. Nester CM, *et al.* ASN Kidney Week 2024. 6. ClinicalTrials.gov. VALE. https://clinicaltrials.gov/study/NCT05809531. Accessed 4 August 2025.

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