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

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CONCLUSIONS

Pegcetacoplan demonstrated sustained safety and efficacy through Week 52 in the phase 3 VALIANT trial in patients with C3G and primary IC-MPGN:

- At Week 52, patients receiving pegcetacoplan showed a **67.2% reduction** in proteinuria from baseline.
- **Estimated glomerular filtration rate (eGFR) remained stable (–3.7 mL/min/1.73 m²)** among patients who received pegcetagoplan for 52 weeks.
- Pegcetacoplan was **well tolerated, with no new safety signals. Four infections caused by encapsulated bacteria** were reported during the open-label period; **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 downstream activation of the complement cascade in C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN).[1–7]
- VALIANT evaluated the use of pegcetacoplan for treatment of C3G and primary IC-MPGN.[8,9]
- Week 26 data for the VALIANT phase 3 study (NCT05067127) demonstrated a slowing of disease progression with pegcetacoplan in adult and adolescent patients with C3G or primary IC-MPGN. Results were published previously.[8]

OBJECTIVE

- Here, we report Week 52 VALIANT safety and efficacy data for patients with C3G and primary IC-MPGN.

METHODS

- Adolescent (12–17 years) and adult (≥18 years) patients were randomized 1:1 to receive up to 1080 mg pegcetacoplan subcutaneously (SC) twice weekly* or placebo for 26 weeks.
- The 26-week double-blind randomized controlled period (RCP) was followed by a 26-week open-label period (OLP) during which all patients received pegcetacoplan up to 1080 mg SC twice weekly.* In both arms, patients also received stable, optimized supportive care.† Patients who completed VALIANT were eligible to enter the VALE extension study.[9]
- Study eligibility criteria have been published previously.[8]
- Endpoints assessed from baseline to Weeks 26 and 52 were:
  - Log-transformed ratio of urine protein-to-creatinine ratio (UPCR).
  - Proportion of participants 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 participants with a reduction of ≥50% in UPCR.
  - Change in eGFR from baseline.
  - Treatment-emergent adverse events (TEAEs).

RESULTS

Patient Characteristics

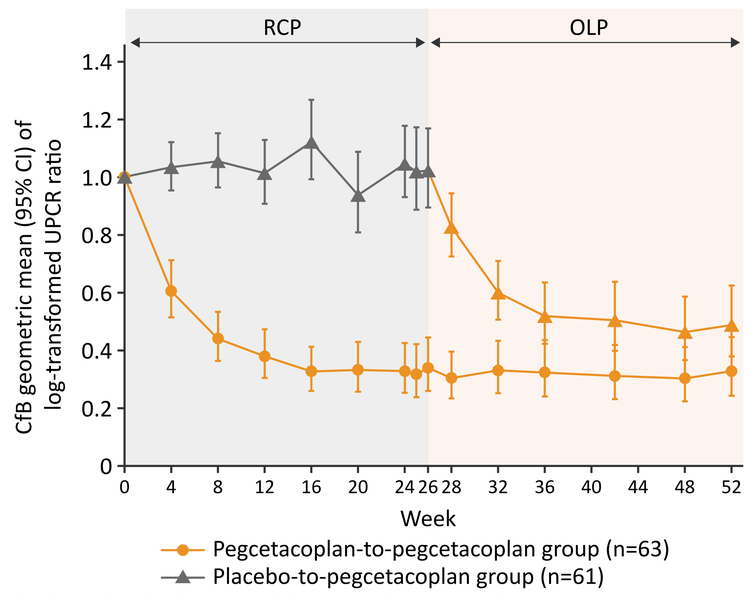
- VALIANT included a broad patient population aged ≥12 years, with native or post-transplant kidneys, and diagnosed with C3G or primary (idiopathic) IC-MPGN. Demographics and clinical characteristics of the 26-week VALIANT study have been published previously.[8]
- In the placebo group, 57 (93.4%) patients 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

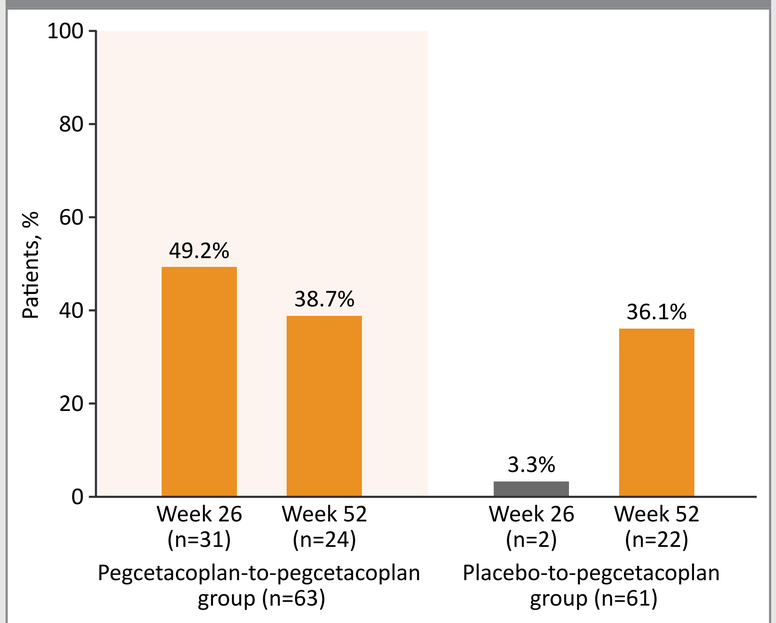
- In pegcetacoplan-treated patients, proteinuria reductions were observed as early as Week 4 with a statistically and clinically significant reduction at Week 26 compared with placebo (relative reduction‡ [95% CI] versus placebo: 68.1% [57.3, 76.2], *P*<.0001)[8] (**Figure 1**).
- This trend was maintained until Week 52 (mean CfB, 67.2%) (**Figure 1**).
- 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**).

Figure 1: Change in proteinuria



CfB, change from baseline; CI, confidence interval; OLP, open-label period; RCP, randomized controlled period; UPCR, urine protein-to-creatinine ratio.

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



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

Composite renal endpoint

- At Week 26, the composite renal endpoint was achieved by significantly more patients on pegcetacoplan vs placebo (31 [49.2%] vs 2 [3.3%]; *P*≤.0001)[8] (**Figure 2**). At Week 52, the composite renal endpoint was met by 38.7% (n=24) of patients in the pegcetacoplan-to-pegcetacoplan group and 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*<.0001)[8] (**Figure 3**). At Week 52, this endpoint was achieved in 50.8% (n=32) of patients in the pegcetacoplan-to-pegcetacoplan group and 41% (n=25) in the placebo-to-pegcetacoplan group (**Figure 3**).

eGFR

- At Week 26, pegcetacoplan stabilized eGFR vs placebo (LS mean change (95% confidence interval [CI]): –1.5 [–5.9, 2.9] vs –7.8 [–11.6, –4.0]; nominal *P*<.05), equating to a difference of +6.3 mL/min/1.73 m² (nominal *P*=.03)[8] (**Figure 4**).
- This trend was sustained through Week 52 (mean CfB, –4.7 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, –3.7 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 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.

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

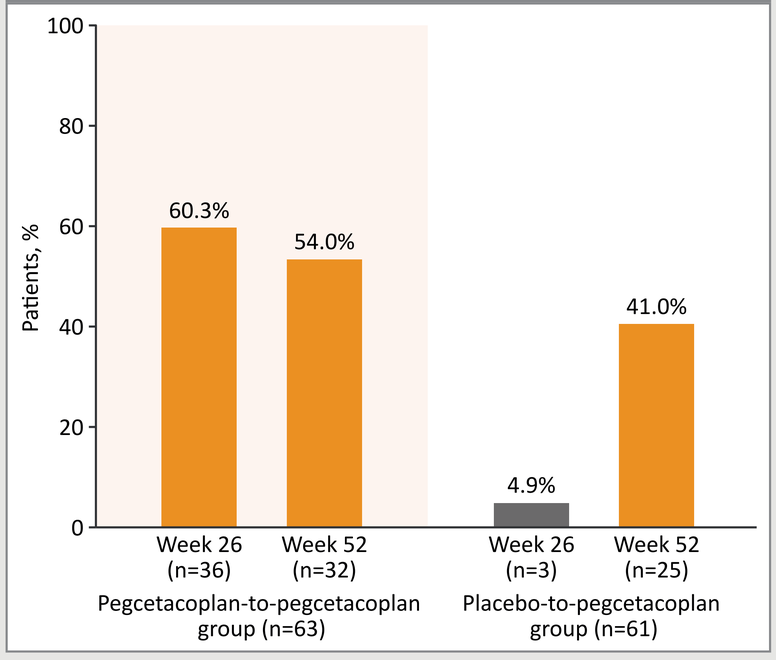
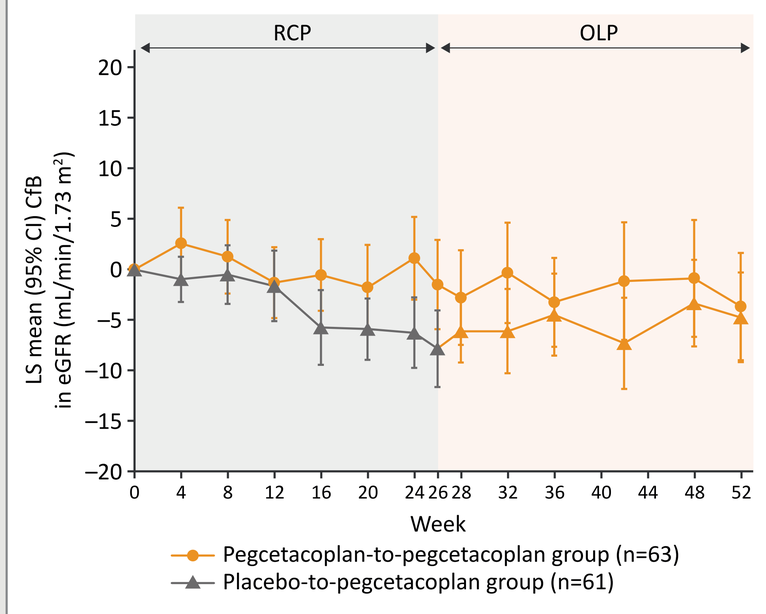


Figure 4: Change in eGFR



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

- 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 of the cases 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 (3.4)
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 (1.8)
TEAE leading to death	1 (1.6)	0	0
Rejection episodes	0	1 (1.6)	0
Graft loss	0	0	0

OLP, open-label period; RCP, randomized controlled period; TEAEs, treatment-emergent adverse events.

*All adults and adolescents weighing ≥50 kg self-administered 1080 mg/20 mL. Adolescent patients weighing 30–34 kg received 540 mg/10 mL for the first 2 doses, then 648 mg/12 mL. Adolescent patients weighing 35–49 kg received 648 mg/12 mL for the first dose, then 810 mg/15 mL. †Stable, optimized antiproteinuric regimens: ACEis, ARBs, SGLT2is, MMF, and corticosteroids (prednisone ≤20 mg/d or equivalent) were permitted. ‡Percentages calculated by converting the ratio of geometric means to percentages.

Abbreviations: ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; 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, randomized controlled period; SC, subcutaneous; SGLT2is, sodium-glucose cotransporter-2 inhibitors; TEAEs, treatment-emergent adverse events; UPCR, urine protein-to-creatinine ratio.

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