VALIANT: Pegcetacoplan for C3G or primary (idiopathic) IC-MPGN

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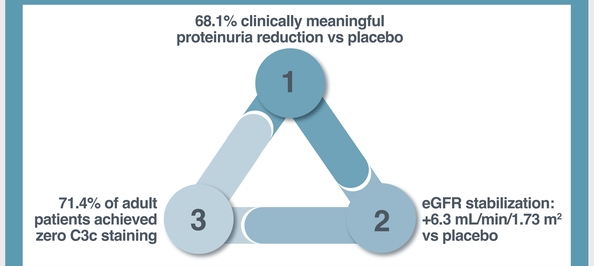
WHAT DID WE LEARN FROM THIS STUDY?

- **In VALIANT, pegcetacoplan demonstrated clinical benefit for adult and adolescent patients with C3G or primary IC-MPGN**
- **Pegcetacoplan was well tolerated by most patients**



- **Proteinuria reduction and eGFR stabilization among all patient subgroups were consistent with those of the full population: C3G vs IC-MPGN, adolescents vs adults, post-transplant vs native kidney disease**

WHY WAS THIS STUDY NEEDED?

- C3G and primary IC-MPGN damage glomeruli[1–3]
  - These disorders are caused by overactivation of part of the immune system called the complement cascade
  - This overactivation can lead to the breakdown of the C3 protein and the activation of the complement cascade
  - These breakdown products can collect in the kidney and cause damage and inflammation
  - Both diseases are diagnosed on the basis of C3 deposits in the kidney
- Pegcetacoplan is a medicine that blocks C3 and C3b, which may prevent further deposition of C3 breakdown products, preventing kidney damage[4–10]

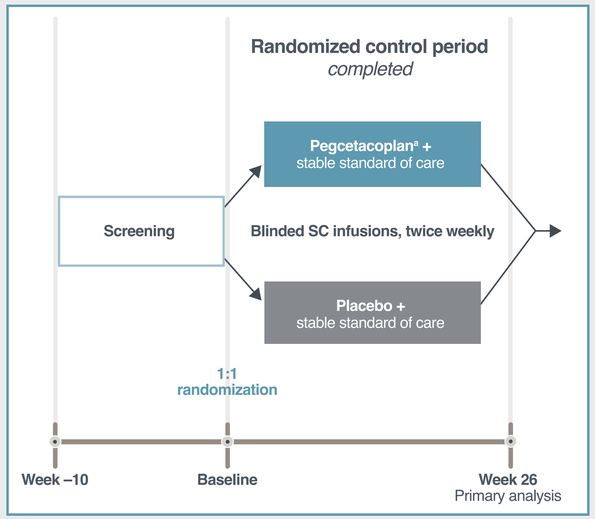
WHAT WAS THE GOAL OF THE STUDY?

The VALIANT study investigated pegcetacoplan for adolescents and adults to learn if it was safe and effective for treating C3G or primary IC-MPGN[11,12]

HOW WAS THIS STUDY CONDUCTED?

- Adolescent (12–17 years) and adult (≥18 years) patients were randomly divided into 2 groups. One group received weight-based pegcetacoplan SC twice weekly and the other received placebo for 26 weeks (**Figure 1**)
- Researchers measured the amount of protein in patients' urine (proteinuria) at the beginning of the study and every 4 weeks after that. They also measured kidney function by calculating eGFR and observing the amount of C3c in the glomeruli using a staining technique called immunofluorescence. C3c staining was conducted only for adults; to participate in the study, patients must have had at least 2+ C3c staining at baseline (measured on a relative scale of 0 to 3)
- Researchers also monitored patients for side effects

FIGURE 1. VALIANT STUDY DESIGN

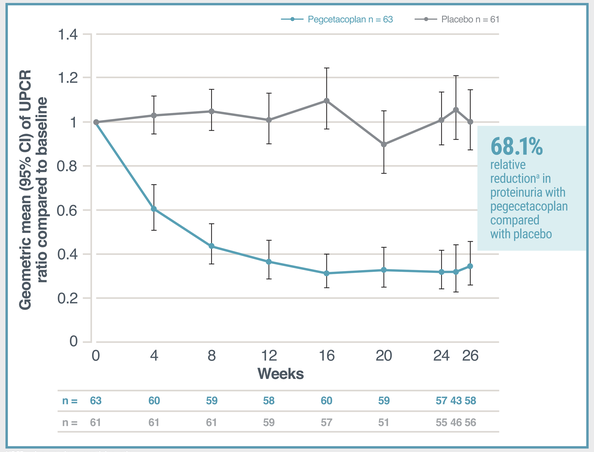


SC, subcutaneous.
[a]Patients weighing ≥50 kg received 1080 mg/20 mL; patients weighing 30–34 kg received 540 mg/10 mL for 2 doses, then 648 mg/12 mL; and patients weighing 35–49 kg received 648 mg/12 mL for 1 dose, then 810 mg/15 mL.

WHAT WERE THE RESULTS OF THE STUDY?

- 63 patients received pegcetacoplan and 61 received placebo
- Most patients (96/124 [77.4%]) had C3G
- On average, patients were in their 20's and more than half were female
- Slightly less than half of patients (44.4%) were adolescents
- Patients receiving pegcetacoplan had decreased (improved) proteinuria within 4 weeks (**Figure 2**)
- After 26 weeks, the pegcetacoplan group had a 68% relative reduction in proteinuria compared with placebo. The difference between pegcetacoplan and placebo was significant (*P* <.0001)

FIGURE 2. CHANGE IN PROTEINURIA (WEEK 26 VS BASELINE)

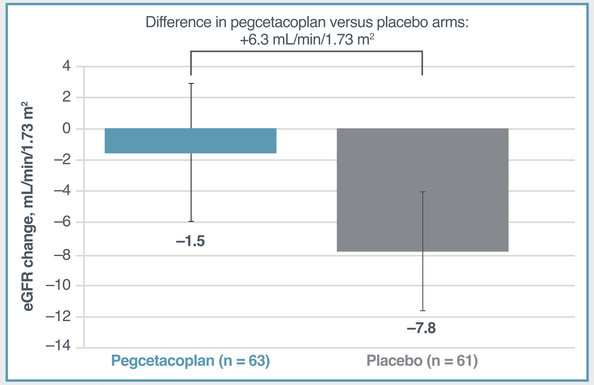


UPCR, urine protein-to-creatinine ratio.
[a]Calculated using the geometric means ratio of pegcetacoplan vs placebo, which was estimated by the exponentiated least-squares means and differences using a composite contrast of equal-weighted average over weeks 24, 25, and 26.

- Patients who received pegcetacoplan also had stable eGFR (**Figure 3**), which suggests that kidney function did not worsen. The change in eGFR with pegcetacoplan was significantly better than with placebo (nominal *P* = .0333)

WHAT WERE THE RESULTS OF THE STUDY? – cont'd

FIGURE 3. CHANGE IN eGFR (WEEK 26 VS BASELINE)



eGFR, estimated glomerular filtration rate.

- Most adult patients in the pegcetacoplan group (26/35 [74.3%]) had decreased C3c staining, compared with 4/34 (11.8%) patients in the placebo group. This difference was significant compared to placebo (nominal *P* < .0001). The likelihood of achieving a staining reduction was 27 times greater with pegcetacoplan than with placebo. Twenty-five patients (71.4%) achieved zero staining intensity
- Nearly all patients experienced side effects, but most were not serious (**Table 1**)
- One patient receiving pegcetacoplan died during the study, but the death was caused by COVID-19 pneumonia (a lung infection) and was not related to pegcetacoplan

TABLE 1. SIDE EFFECTS

	Pegcetacoplan (n = 63)	Placebo (n = 61)
Any side effect, n (%)	53 (84.1)	57 (93.4)
Serious side effect, n (%)	6 (9.5)	6 (9.8)
Side effect leading to study discontinuation, n (%)	1 (1.6)	1 (1.6)

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References: **1.** Pickering MC, et al. *Kidney Int* 2013;84(6):1079–89; **2.** Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100(4S):S1–276; **3.** Vivarelli M, et al. *Kidney Int* 2024;106(3):369–91; **4.** Smith RJH, et al. *Nat Rev Nephrol* 2019;15:129–43; **5.** Zipfel PF, et al. *Front Immunol* 2019;10:2166; **6.** Meuleman MS, et al. *Semin Immunol* 2022;60:1016342; **7.** Dixon BP, et al. *Kidney Int Rep* 2023;8:2284–93; **8.** EMPAVELI® (pegcetacoplan) US PI 2024; **9.** ASPAVELI Summary of Product Characteristics 2024; **10.** Lamers C, et al. *Nat Commun* 2022;13:5519; 11. Dixon BP, et al. ASN Kidney Week 2023, Nov 2–5, 2023; 12. ClinicalTrials.gov. VALIANT. clinicaltrials.gov/study/NCT05067127. Accessed Sep 18, 2024.

Abbreviations: C3, complement component 3; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; SC, subcutaneous; UPCR, urine protein-to-creatinine ratio.

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